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EVIDENCE-BASED MEDICINE, CLINICAL TRIALS AND THEIR INTERPRETATIONS (L. ROEVER, SECTION EDITOR)

Analyzing Preeclampsia as the Tip of the Iceberg Represented by Women with Long-Term Cardiovascular Disease, Atherosclerosis, and Inflammation

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Abstract

Purpose of Review Cardiovascular and endothelial dysfunction is recognized nowadays as an important etiological factor contributing to the development of hypertensive disorders of pregnancy.

Recent Findings Preeclampsia is considered a specific disease of pregnancy, but recent theories suggest that women suffering from the condition have greater propensity to develop atherosclerosis, heart disease, and stroke over the years.

Summary It is possible that transient but severe endothelial dysfunction observed in preeclampsia potentiates a cascade of events that progresses to atherosclerosis. Preeclampsia offers a unique window of opportunity to identify maternal endothelial dysfunction and pre-existing cardiovascular disease. The placenta is closely involved in the onset of preeclampsia, but endothelial and cardiac vascular factors also play important causal roles in the development of hypertension during pregnancy. According to the data presented, it is clear that preeclampsia selects a group at high risk of development of atherosclerosis and at increased cardiovascular risk, as well as of stroke, in the decades following childbirth.

Keywords Preeclampsia · Eclampsia · Hypertensive disorders · Gestation · Inflammation · Atherosclerosis · Arterial stiffness · Cardiovascular risk · Endothelial dysfunction · Ophthalmic artery · Doppler

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Introduction

A Brief History of Preeclampsia/Eclampsia

Preeclampsia (PE) has been known and studied since ancient Greece, between the late fifth and early fourth centuries BCE, when Hippocratics subscribed to the theory of the four humors to describe the cause of illness and disease. However, this disease was not formally classified as a disorder of pregnancy at that time [1]. During the Middle Ages, medical and scientific progress came to a standstill but was resumed during the Renaissance [1]. Studies on the disease have progressed, and the word "eclampsia," which derives from the Greek term "lightning," first appeared in 1619 in Varandeau's treatise on gynecology [2, 3]. In the twentieth century, although researchers still failed to uncover the etiology of preeclampsia/eclampsia, much progress has been made in the understanding of the associated pathophysiological changes.

In the present twenty-first century, the scientific community has failed to uncover all the etiologic mechanisms responsible for the development of preeclampsia ; theories on disease causation are numerous and diverse. There are many hypotheses to explain the etiology of preeclampsia , although a single explanation for the disease is unlikely [4–10]. Currently, the most important pathogenesis involves deficient placentation, genetic predisposition, impaired immune tolerance, systemic inflammatory response, angiogenic imbalance, and deficient nutritional status [11, 12]. Although still considered a specific disease of pregnancy, recent theories suggest that women who have suffered PE are more at risk of developing atherosclerosis, heart disease, and stroke over the years [13–15]. Besides that, cardiovascular and endothelial dysfunction are nowadays recognized as important etiological factors contributing to the development of hypertensive disorders of pregnancy [16••].

Epidemiology

Preeclampsia is a major cause of maternal mortality (15–20% in developed countries) and of acute and long-term morbidities such as perinatal deaths, preterm births, and intrauterine growth restriction [17]. This disease occurs in an estimated 1 in 20 pregnancies and can develop into eclampsia, which account for up to 10% of maternal deaths [18]. An estimated 50,000 women worldwide die annually from preeclampsia , and the incidence of preeclampsia is 2–10%, depending on the population studied and the definition of preeclampsia . In Brazil, the mortality rate among all pregnant women from eclampsia was 19% and ranks fifth of all studied causes; other hypertensive pregnancy diseases were in seventh place, at 10.7% [19]. Preeclampsia also is the main cause of elective prematurity in Brazil [20]. Regarding long-term risks, in the first year after delivery, women with hypertensive disorders of pregnancy had 12- to 25-fold higher rates of hypertension than women with a normotensive pregnancy. Rates in women with a hypertensive disorder of pregnancy were three- to tenfold higher with 1–10-year postpartum and remained twice as high even 20 or more years later [21]. The history of preeclampsia is also associated with a six- to sevenfold increased hazard of suffering a recurrent ischemic attack within 1 year of developing acute coronary syndrome [22]. Women with a diagnosis of preeclampsia have an increased risk of cardiovascular disease, including an almost fourfold increased risk of hypertension and an approximately twofold increased risk of fatal or non-fatal ischemic heart disease, stroke, and venous thromboembolism in later life, which suggests a specific relationship between preeclampsia and cardiovascular disease [15].

Preeclampsia : Concept and Classification

The recommended classification of hypertensive disorders during pregnancy is chronic hypertension, gestational hypertension, preeclampsia/eclampsia, and chronic hypertension with superimposed preeclampsia [23]. For the current clinical practice, we consider the four forms described below, always with blood pressure ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic:

1. Chronic hypertension: Presence of hypertension before pregnancy or identified before 20 weeks gestation.
2. Preeclampsia: New onset of hypertension after the 20th week of gestation associated with significant proteinuria. The classification of proteinuria is the presence of at least 300 mg in 24-hour urine or urinary protein/creatinine ratio ≥ 0.3 (units of both proteinuria and creatinine should be in mg/dL). If it is not possible to determine proteinuria by the previous methods, the qualitative evaluation of protein by a dipstick test can be considered. The presence of + 1 is considered as the cutoff for the diagnosis of proteinuria, an identification compatible with ~ 30 mg/dL [23]. Although this association is classically recognized, currently the presence of proteinuria is not mandatory for the diagnosis of preeclampsia. If hypertension after the 20th week is associated with systemic impairment or target organ damage (thrombocytopenia, hepatic dysfunction, renal failure, pulmonary edema, imminent eclampsia, or eclampsia), the disease should be diagnosed even in the absence of proteinuria.The association of arterial hypertension with signs of placental impairment, such as fetal growth restriction and/or Doppler velocimetric changes, should also call attention to the diagnosis of preeclampsia, even in the absence of proteinuria [24]. Preeclampsia with signs and/or symptoms of clinical deterioration is considered based on the following criteria:

(a) Hypertensive crisis: BP ≥ 160 mmHg and/or 110 mmHg.
(b) Signs of imminent eclampsia: In this case, patients present a clear nervous system compromise and report headache, photophobia, phosphenes, and scotomas. The presence of nausea and vomiting, epigastric pain, and/or pain in the right hypochondrium is very important and is related to hepatic impairment.
(c) Eclampsia: Development of tonic–clonic seizures in patients with a diagnosis of preeclampsia.
(d) Hemolysis, elevated liver enzymes, and low platelets are classified as HELLP syndrome. The aforementioned changes are defined as follows: Hemolysis, the presence of schizocytes and echinocytes in the peripheral blood, and/or elevation of lactate dehydrogenase (LDH) levels to > 600 UI/L and/or indirect bilirubin at > 1.2 mg/dL and/or haptoglobin at ≤ 0.3 g/L; hepatic impairment determined by elevation of aspartate aminotransferase

(AST) and alanine aminotransferase (ALT) values at greater than twice their normal value; and platelet count defined as < 100.000/mm^3.
(e) Oliguria: Diuresis < 500 mL/24 h.
(f) Acute renal failure: Serum creatinine ≥ 1.2 mg/dL.
(g) Thoracic pain.
(h) Pulmonary edema.

3. Chronic hypertension with superimposed preeclampsia: This diagnosis must be established in some specific situations. (a) After 20 weeks gestation, there is onset or worsening of proteinuria already detected in the first half of pregnancy (the increase must be greater than three times the initial value); (b) pregnant women with chronic hypertension who need an association of antihypertensive drugs or an increase in initial therapeutic doses; and (c) the occurrence of target organ damage.
4. Gestational hypertension: Identification of arterial hypertension after the 20th week of gestation in a previously normotensive pregnant woman without proteinuria or manifestation of other signs/symptoms related to preeclampsia. This form of hypertension should disappear up to 12 weeks after childbirth. If blood pressure levels remain elevated, it should be reclassified as chronic arterial hypertension masked by physiological changes of the first half of pregnancy. Considering the current concepts of the diagnosis of preeclampsia, even in the absence of proteinuria, one must always be aware of the possibility of unfavorable evolution of cases initially diagnosed as gestational hypertension, since up to 25% of these patients will present signs and/or related symptoms of preeclampsia, thus altering their diagnosis [25].

Preeclampsia is commonly categorized into two clinically distinct phenotypes: considering the gestational age at the clinical manifestation of preeclampsia, the disease can be classified as early (< 34 weeks) or late (≥ 34 weeks). Early-onset preeclampsia is generally associated with increased impairment of placental development and uteroplacental circulation, abnormal Doppler velocimetric evaluation of uterine arteries, fetus growth restriction, and worse maternal and perinatal outcomes [25]. This is commonly explained as a reflection of the marked importance of placentation in the development of early-onset preeclampsia [16••]. Late-onset preeclampsia is often associated with metabolic syndromes, inflammation, and chronic endothelial impairment. Thus, its association with obesity and chronic diseases is common. The uteroplacental compartment is often within the normal range or changes little. Maternal and perinatal outcomes are more favorable, mainly because these manifestations are closer to term, and the prevalence of adverse maternal outcomes is approximately 10% for late-onset and 15% for early-onset preeclampsia [26].

Preeclampsia as Pregnancy-Specific Acute Illness

As an acute illness in pregnancy, preeclampsia occurs in two stages: (1) abnormal placentation early in the first trimester, followed by (2) a "maternal syndrome in the later second and third trimesters characterized by an excess of antiangiogenic factors" [27,28]. A number of theories have been proposed for the placental dysfunction observed in Stage 1, including oxidative stress, abnormal natural killer (NK) cells at the maternal–fetal interface, and genetic and environmental factors, although there is no conclusive evidence in humans [29]. There is substantial evidence to support that a diseased placenta leads to the release of soluble toxic factors into the maternal circulation, which results in inflammation, endothelial dysfunction, and maternal systemic disease [27,28]. Despite the theories supported above, it is known that antiangiogenic state does not always result in the development of preeclampsia. There are no concrete explanations but is possible that preeclampsia develops according to the threshold of angiogenic imbalance is reached in each pregnant woman individually. Probably the constitutional maternal predisposition associated with severe endothelial insult becomes necessary for the development of the preeclampsia. Thus, the most seriously defective placentation causes cellular stress, with the subsequent release of extremely high amounts of sFlt-1 by syncytiotrophoblast, leading to preeclampsia. So the prognosis for women with PE varies depending on their underlying relation to placental damage, angiogenic state, and maternal susceptibility [30].

Early-onset preeclampsia ("before 34 weeks," usually associated with abnormal uterine artery Pulsatility Index Doppler, fetal growth restriction, adverse maternal and neonatal outcomes, increased relative maternal wall thickness, and small left ventricular diameter at 24 weeks gestation) appears to be linked mainly to failed placental vascular remodeling, which expresses itself through a high total vascular resistance and low cardiac outcome. Late-onset preeclampsia ("after 34 weeks," usually associated with normal or minor increased uterine resistance index, low rate of fetal involvement and more favorable perinatal outcomes, and maternal left ventricular underfilling state with pressure overload) might be linked to maternal constitutional factors and is characterized by a low total vascular resistance with high cardiac output. Thus, early-onset preeclampsia appears to be more related to the evolution of a highly altered cardiovascular response probably triggered by a placental disorder. Late-onset preeclampsia seems to be more linked to maternal constitutional factors. Because early and late preeclampsia seems to be different hypertension diseases, some authors compared maternal cardiac function, and uterine artery Doppler, in a group of 1345 nulliparous normotensive asymptomatic women at 24 weeks of gestation, calculating total vascular resistance. In the subsequent follow-up,

107 patients developed PE, divided into 32 patients with late preeclampsia and 75 with early preeclampsia. Comparing both groups, they observed in early preeclampsia more patients with bilateral notching of the uterine artery at 24 weeks; higher total vascular resistance and lower cardiac output; and lower prepregnancy body mass index. Until 1-year postpartum, both early and late preeclampsia are characterized by hypertrophied ventricles versus controls, although late preeclampsia shows larger left ventricle diameter than does early-preeclampsia. They concluded that it is probable that both forms of preeclampsia have different etiologies and different models of maternal cardiovascular adaptation in the latent phase of the disease and postpartum, showing two drastically different hemodynamic states at 24 weeks gestation [31].

Maternal Cardiovascular Adaptation in Preeclampsia and Normal Pregnancy

Considering the role of the cardiovascular system in the development of preeclampsia, it is important to understand how cardiovascular adaptation occurs during pregnancy. It is known that pregnancy is characterized by massive cardiovascular changes, starting as early as the first trimester and becoming overloaded during the third trimester. In normal pregnancy, there is an increase of approximately 1500 ml in blood volume, associated with reduced vascular compliance and increased cardiac output of around 30–40% in order to maintain normal mean arterial blood pressure [16••, 32].

There are conflicts around the functional changes in heart musculature and other echocardiographic indices. In a large cohort study of 559 normal and non-obese pregnant women who underwent cardiovascular assessment, Melchiorre et al. (2016) showed an increase of 40% in ventricular myocardium mass at term compared to non-pregnant women. The authors demonstrated that despite women having an apparently normal pregnancy, 2–5% of them showed signs of ventricular dysfunction (altered cardiac geometry, radial and longitudinal systolic dysfunction) and approximately one in six showed mildly impaired diastolic function [33••]. Therefore, it is understood that pregnancy is a period of cardiovascular overload, which could be a trigger for the decompensation of subclinical cardiovascular diseases in a group of pregnant women considered normal [33••].

Regarding cardiovascular maladaptation during pregnancy and the development of hypertensive diseases, there are some studies described in the literature. A systematic review published by Castelman et al., analyzed the echocardiographic assessment of structure and functional in hypertensive disorders of pregnancy, using and identified in preeclampsia: increase total vascular resistance; no change in ejection fraction; exaggerated reduction in E/A; increased left ventricular mass in gestational hypertension and increased total vascular resistance; decreased stroke volume; exaggerated reduction in E/A and increased E/e'; and increased left ventricular mass. This systematic review demonstrates that cardiac structure and function identified by echocardiography are altered in the preclinical and clinical phases of gestational hypertension and preeclampsia. For women with preeclampsia, diastolic dysfunction and increased peripheral vascular resistance correlate with disease severity. Recognition of impairment in cardiac function is important in the contemporary management of gestational hypertension and preeclampsia to improve pregnancy outcomes and long-term cardiovascular health [32].

In a prospective study by Timokhina et al., 90 puerperal women with preeclampsia and previous eclampsia and 50 normal puerperal women were analyzed by echocardiography for hemodynamic evaluation in the early postpartum period and after 2 and 6 months. Hemodynamic behavior was significantly different between the two groups of postpartum women. The echocardiographic parameters demonstrated in puerperal women with preeclampsia and eclampsia showed increased vascular resistance and significant reduction in myocardial contractility, which may represent asymptomatic heart failure. The authors therefore concluded that women who present preeclampsia remain impaired. These data are consistent with the findings that patients with preeclampsia are at high risk of developing long-term cardiovascular complications [34].

In an observational prospective study, Simmons et al. analyzed the echocardiographic examinations of 15 women with preeclampsia, and 12 non-pregnant and 44 normally pregnant women, during the trimesters and postpartum. They described that pregnancy is associated with hemodynamic and hormonal changes that can affect the heart, but that during normal pregnancy the myocardial contractile function is not significantly altered. Cardiac remodeling involving eccentric hypertrophy, enlargement of the chambers, and thickening of the left ventricular wall was observed during pregnancy, and exaggerated ventricular hypertrophy with unchanged systolic function was observed in preeclamptic women. These changes in cardiac geometry were rapidly reversible within 3 months of birth in normotensive women, but resolution remained incomplete in preeclamptic women, demonstrating vulnerability in the latter group [35].

Vascular maladaptation in puerperal women with previous preeclampsia was observed through the ophthalmic artery Doppler study by Borges et al. A prospective cohort study was conducted with 44 postpartum women with previous preeclampsia, compared to 49 postpartum women with normal blood pressure and no previous disease. The patients were evaluated at three times, including the immediate, late, and remote puerperium. During pregnancy there were signs of vasodilation, hyperperfusion, and increase in the second peak systolic velocity of the ophthalmic artery flow velocity wave

in women with preeclampsia. The authors described the persistence signs of vasodilation and hyperperfusion in the orbital territory of preeclamptic women during the immediate postpartum period. There was a tendency to normalize the arterial vascular pattern of the ophthalmic artery in pregnant women with preeclampsia from later on, but there was incomplete normalization of the vascular pattern in the remote postpartum. This behavior demonstrated that preeclamptic women are susceptible to hemodynamic vascular disease, with abnormal arterial reactivity [36].

With the understanding that vascular response of the ophthalmic artery is altered in pregnant women with preeclampsia and that vasodilation does not return to normal in the postpartum period, we can interpret that maladaptation corresponds to a predisposition risk factor that remains for the development of vascular diseases in the future.

Regarding the similarities of vascular responses of arterial hypertension and coronary flow reserve in women with PE in pregnancy and postpartum, ophthalmic artery Doppler shows a common change in the waveform: an increase in the second diastolic peak preceding the dicrotic notch in all these situations, which may suggest a common behavior in vascular remodeling for these subjects [36–38]. Arterial waveform is the result of the summation of the incident wave traveling toward the periphery combining with the reflected wave returning from the periphery; thus, the increased second peak may be reflected by the early wave returning over the systole resulting from increased arterial [39].

Association Between Preeclampsia With Endothelial Function and Long-Term Risk of Atherosclerosis x Cardiovascular Disease

One concept of endothelial disorder in pregnancy is based on poor endothelial function affecting placental perfusion and predisposing to preeclampsia. This theory is supported by recent studies on pregnancy-related hormones as mediators of vascular growth and endothelial health [16••]. Clinically, preeclampsia can present two steps: Stage 1 reduced placental perfusion, and in some, but not all, women progressing to Stage 2, a multisystem maternal syndrome can exhibit reduced liver and adrenal perfusion, endocardial necrosis, marked swelling of kidney glomerular endothelial cells, and even death [40]. In pregnancy, transformation of the spiral arteries is necessary, when they suffer dramatic structural changes, dilation of the lumen, invasion of the trophoblast into the vessel wall, and replacement of the muscular and elastic tissue of the arterial wall by a thick fibrinoid material, which must occur during the first 3 months. Preeclampsia presents failure of these physiological remodelings, retaining thick walls and a narrow lumen and remaining prone to developing acute atherosis. The idea that acute atherosis in the placenta may increase the risk of future cardiovascular disease in women with a history of preeclampsia is of growing concern, supporting that similarities between preeclampsia and atherosclerosis, as well as between acute atherosis of the spiral arteries and coronary atherosclerosis, have been observed, and chronic vascular inflammation is one of the main causes of both [13]. During normal pregnancy, to suppress the maternal immune system tolerance for the semi-allogenic fetal antigens must be established while maintaining immune protection against pathogens. Thus, normal pregnancy proceeds with mild inflammation. Women with PE exhibit chronic immune activation and have an exaggerated innate inflammatory response. This pro-inflammatory status in PE could play a role in long-term sequelae, such as stroke or other cardiovascular events [41].

Some investigations have shown several factors, including activation of inflammatory cells and immunological responses, in which neutrophils, lymphocytes, and thrombocytes participate by releasing inflammatory cytokines and autoantibodies in patients with preeclampsia. This suggests that these inflammatory markers could be useful in the prediction of preeclampsia [42].

We know that atheromatosis carries characteristics of low-grade local systemic inflammation, but there is some doubt as to whether these changes are only related to an epiphenomenon. However, the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) showed evidence that neutralizing interleukin-1 by the use of a selective antibody resulted in a significant reduction in cardiovascular events without interfering with LDL and cholesterol levels. This information will certainly stimulate new lines of research into the subject, with the possibility of promoting the discovery of new treatments for atheromatosis and inflammation [43].

It is interesting to note that cigarette smoking protects women from the onset of preeclampsia. Smoking is associated with lower maternal sFlt-1 concentrations during pregnancy and preeclampsia. Based on these data, exposure to cigarette smoke may decrease the risk of preeclampsia, in part by moderating the anti-angiogenic phenotype observed in the syndrome [44,45].

A history of preeclampsia should be considered when evaluating the risk of cardiovascular disease in women. It increases the risk of future hypertension, ischemic heart disease, stroke, venous thromboembolism, and death from any cause. It is likely that women who have recurrent preeclampsia have an underlying pathological phenotype that puts them at risk of hypertension and cardiovascular disease. It is possible that transient but severe endothelial dysfunction observed in preeclampsia potentiates a cascade of events that progresses to atherosclerosis [46]. Preeclampsia offers a unique window of

opportunity to identify maternal endothelial dysfunction and pre-existing cardiovascular disease [47].

It is established that preeclampsia is an independent risk factor for subsequent long-term atherosclerotic complications, including cardiovascular and renal complications requiring hospitalization. The risk is more substantial for patients with severe and recurrent episodes of preeclampsia [48].

Some authors have associated early gestational age at the onset of preeclampsia with subclinical atherosclerosis. Christensen et al. described that gestational age at preeclampsia onset is negatively associated with markers of subclinical atherosclerosis 12 years after delivery. They concluded that, potentially, gestational age at preeclampsia onset might be helpful in directing cardiovascular disease prevention after preeclampsia [49].

Milic et al. conducted a systematic review and meta-analysis with the objective of determining whether women with preeclampsia have increased atherosclerotic burden, as determined by carotid intima-media thickness, when compared to women who did not have preeclampsia. Most of the studies evaluated in the meta-analysis observed that the atherosclerotic burden is present at the time of pregnancy of the patients with preeclampsia. Therefore, it seems that atheromatosis is involved in the complex mechanism of the development of preeclampsia. Based on this theory, the patient with preeclampsia would already be classified at risk of the development of cardiovascular diseases in the premenopausal period. Moreover, they suggested the study of the use of statins in the treatment of preeclampsia, aiming at reducing endothelial dysfunction, and consequently adverse cardiovascular events, in the future [50•].

Prevention of Preeclampsia

The first insight into the aspirin action reducing preeclampsia was described in 1979. In this study, the women who had taken aspirin regularly during pregnancy were less likely to have preeclampsia than pregnant women who had not [51]. An important study was published in 2017 that established the use of a combined multimarker screening and randomized patient treatment with aspirin trial, among women of high risk for preterm preeclampsia, aspirin at a dose of 150 mg per day, taken from 11 to 14 weeks of gestation until 36 weeks of gestation, would result in an incidence of preterm preeclampsia that was half the incidence observed with placebo [52]. A systematic review and meta-analysis with 16 trials that included 18,907 participants provided data for preterm and term preeclampsia concluded that aspirin reduces the risk of preterm preeclampsia, but not term preeclampsia, and only when it is initiated at ≤ 16 weeks of gestation and at a daily dose of ≥ 100 mg [53].

Conclusions

Preeclampsia is a multifactorial and multisystemic disease, specific to the gestational period, but which carries within its pathophysiology cardiovascular risk patterns that manifest during pregnancy due to the overload imposed by it. There is no doubt that the placenta is closely involved in the onset of preeclampsia , but endothelial and cardiac vascular factors also play important causal roles in the development of the clinical form of the disease during pregnancy.

According to data presented in the current review, it is clear that preeclampsia selects a high-risk group for the development of atherosclerosis and increased cardiovascular risk, as well as stroke, over the decades following childbirth.

Therefore, it is important that the medical community does not neglect the careful follow-up of these women throughout their lives in order to encourage activities that protect them from adverse cardiovascular events. This should be a priority in public health policies aimed at increasing the quality of life of these women.

Compliance with Ethical Standards

Conflict of Interest Angélica Lemos Debs Diniz, Maria Marta Bini Martins Paes, and Aline Debs Diniz each declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki Declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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- •• Of major importance

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