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146	Abstract	Pregnancy is a physiologically stressful condition that generates a series of functional adaptations by the cardiovascular system. The impact of pregnancy on this system persists from conception beyond birth. Recent evidence suggests that vascular changes associated with pregnancy complications, such as preeclampsia, affect the function of the maternal and offspring vascular systems, after delivery and into adult life. Since the vascular system contributes to systemic homeostasis, defective development or function of blood vessels predisposes both mother and infant to future risk for chronic disease. These alterations in later life range from fertility problems to alterations in the central nervous system or immune system, among others. It is important to note that rates of morbi-mortality due to pregnancy complications including preeclampsia, as well as cardiovascular diseases, have a higher incidence in Latin-American countries than in more developed countries. Nonetheless, there is a lack both in the amount and impact of research conducted in Latin America. An impact, although smaller, can be seen when research in vascular disorders related to problems during pregnancy is analyzed. Therefore, in this review, information about preeclampsia and endothelial dysfunction generated from research groups based in Latin-American countries will be highlighted. We relate the need, as present in many other countries in the world, for increased effective regional and international collaboration to generate new data specific to our region on this topic.

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PREECLAMPSIA (VD GAROVIC, SECTION EDITOR)

Vascular Dysfunction in Mother and Offspring During Preeclampsia: Contributions from Latin-American Countries

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Abstract Pregnancy is a physiologically stressful condition that generates a series of functional adaptations by the cardiovascular system. The impact of pregnancy on this system persists from conception beyond birth. Recent evidence suggests that vascular changes associated with pregnancy complications, such as preeclampsia, affect the function of the maternal and offspring vascular systems, after delivery and into adult life. Since the vascular system contributes to systemic homeostasis, defective development or function of blood vessels predisposes both mother and infant to future risk for chronic disease. These alterations in later life range from fertility problems to alterations in the central nervous system or immune system, among others. It is important to note that rates of morbi-mortality due to pregnancy complications including preeclampsia, as well as cardiovascular diseases, have a higher incidence in Latin-American countries than in more developed countries. Nonetheless, there is a lack both in the amount and impact of research conducted in Latin America. An impact, although smaller, can be seen when research in vascular disorders related to problems during pregnancy is analyzed. Therefore, in this review, information about preeclampsia and endothelial dysfunction generated from research groups based in Latin-American countries will be highlighted. We relate the need, as present in many other countries in the world, for increased effective regional and international collaboration to generate new data specific to our region on this topic.

Keywords Preeclampsia · Latin-American countries · Vascular dysfunction · Cardiovascular risk · Fetal programming

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Introduction

Preeclampsia is a major cause of maternal and infant morbidity and mortality worldwide [1]. Stillbirth is more common in preeclamptic pregnancies, and one third of infants of preeclamptic women are growth restricted [2, 3] while preterm delivery is twice as common in preeclampsia as in normotensive pregnancies [2]. Furthermore, numerous epidemiological and experimental studies suggest that adverse intrauterine environment is associated with high risk of cardiovascular diseases in adult life in both mothers and their children [4–12].

Endothelial dysfunction is defined as a systemic pathological state characterized by an imbalance between vasodilator and vasoconstrictor effectors, produced by or acting on the endothelium, and has been linked to development of preeclampsia and cardiovascular disease [13, 14]. Indeed, endothelial dysfunction has been considered a key component of preeclampsia pathophysiology since the 1980s [15, 16]. Accordingly, several publications have described endothelial dysfunction, maternal [15–17], in the feto-placental circulation [see details in 18, 19] or in children born to women with preeclampsia [4, 20–22]. However, whether vascular dysfunction observed in these three areas has the same pathophysiology is a question whose answer remains unclear.

In Latin-American countries where preeclampsia is one of the leading causes of maternal and fetal mortality [23], information about this disease has been mainly related to what has been studied in developed countries. This means that information about regional particularities of the disease and its consequences in mothers and their children, or even, the relationship to the future cardiovascular disease, is unknown. In this article, information about preeclampsia and endothelial dysfunction drawn from research groups based in Latin-American countries will be highlighted to illustrate the need for increased international and regional collaborations to search for regional particularities regarding vascular dysfunction in mother and offspring during preeclampsia.

Preeclampsia: General Overview

Diagnostic Criteria

Preeclampsia is a multisystem disorder during pregnancy, generally defined as new onset hypertension and proteinuria, appearing at or after 20 weeks of gestation in a previously normotensive woman [12, 24–27]. The criteria include the presence of gestational hypertension: systolic blood pressure (SBP) > 140/diastolic blood pressure and/or (DBP) > 90 mmHg; proteinuria ≥ 0.3 g protein in 24 h or in the absence of the proteinuria, the presence of headache, blurred vision, epigastric pain, thrombocytopenia (< 100,000/ml) and abnormally high liver enzyme values, as established by the American College of Obstetricians and Gynecologists through the Task Force on Hypertension in Pregnancy [28] (see Box 1). Additionally, renal failure, stroke, cardiac dysfunction or arrest, respiratory compromise, coagulopathy, and liver failure are present in preeclampsia or with severe features. Eclampsia is preeclampsia with seizures. [3, 23]. Recently, the Task Force on Hypertension in Pregnancy [28] eliminated the mild or severe preeclampsia designations; instead, the group adopted the following terms: preeclampsia with or without severe findings.

Most of the Latin-American countries have adopted criteria from American College of Obstetricians and Gynecologists (ACOG) to generate specific guidelines (see Fig. 1). However, differences in the diagnostic criteria between Latin-American countries, although small, reveal the particularities of each country, about which criteria apply to resolve specific issues, and stress the importance of any regional guideline or consensus to be used.

Epidemiology of Preeclampsia: Focus on Latin America

Latin America was able to reduce their maternal mortality rate over the last 20 years, from 114,000 deaths per 100,000 live birth in 1995 to 7900 in 2015 [29] (Fig. 2). This rate is lower in countries such as Puerto Rico and Uruguay, whereas extremely higher rates are still observed in Haiti, Guyana, Suriname, Bahamas, Paraguay, and Bolivia. In this regard, some of these countries have adopted a strategy to provide antenatal care and to continuously follow the mother for at least 6 months after delivery, as an approach to decrease maternal death. The program called *Seguro Universal Materno Infantil* has been proven as a valuable tool for health assistance in Bolivia, since

Box 1 Diagnosis criteria from the American College of Obstetricians and Gynecologists

New-onset of symptoms after 20 weeks' gestation with remission by 6–12 weeks postpartum
The SBP or the DBP ≥ 140/90 mmHg on two occasions at least 4 h apart.
The SBP or the DBP ≥ 160/110 mmHg, confirmed within a short interval (minutes)
and
Proteinuria ≥ 300 mg/24 h
or
Protein/creatinine ratio ≥ 0.3 mg/dl
Dipstick reading of 1+ (without other quantitative methods available)
Or in the absence of proteinuria, any of the following:
Thrombocytopenia: Platelet < 100,000/μl (15–30% of patients)
Renal insufficiency: Serum creatinine concentrations > 1.1 mg/dl or a doubling of the serum creatinine concentration in the absence of other renal disease.
Impaired liver function: elevated blood concentrations of liver transaminases to twice normal concentration.
Pulmonary edema (3% of patients)
Cerebral or visual symptoms
HELLP syndrome
Hemolysis, elevated liver enzymes, and low platelet count
Eclampsia
New-onset grand mal seizures

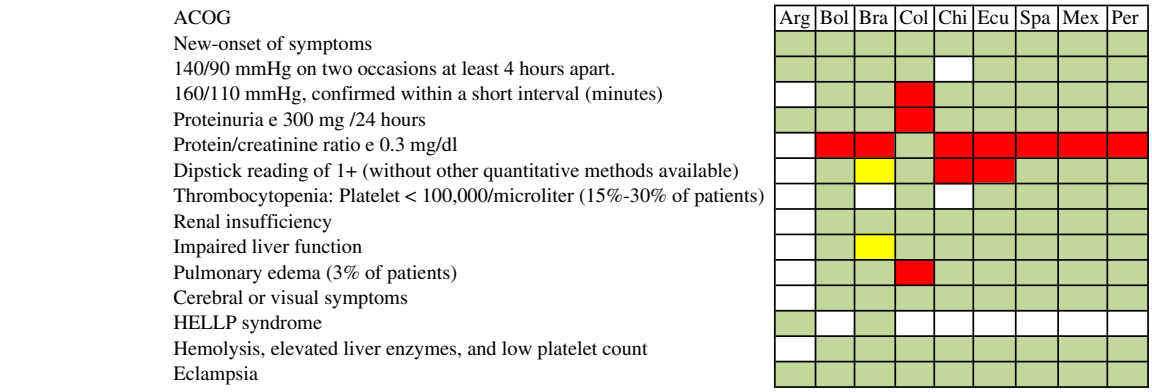


Fig. 1 Percentage of accomplishment of the ACOG diagnosis criteria for preeclampsia in Latin-American countries. For this figure, official guidelines for diagnosis of preeclampsia from Latin-American countries including Argentina (Arg), Bolivia (Bol), Brazil (Bra), Colombia (Col), Chile (Chi), Ecuador (Ecu), Spain (Spain), Mexico (Mex), and Peru (Per) were reviewed. Coincidences between these local guidelines with ACOG guideline are indicated in colors. Inclusion (green), no inclusion (red), partially included (yellow), and no mention (white) of the ACOG guidelines in the local ones are indicated in each color

1996, in a country where only 57% of women given birth within the healthcare system [30].

Hypertensive disorders directly contribute to maternal death and these disorders do not require mandatory reporting in most of the under developed countries. This results in unreliable data, making it extremely difficult to determine the incidence of preeclampsia in those countries. Despite that, depending on the quality of the diagnostic criteria applied, the worldwide incidence of preeclampsia ranges from 3 to 10% of all pregnancies [23, 26]. Each year, it is estimated that hypertensive disorders observed during pregnancy, particularly preeclampsia, complicate 10 million pregnancies, resulting

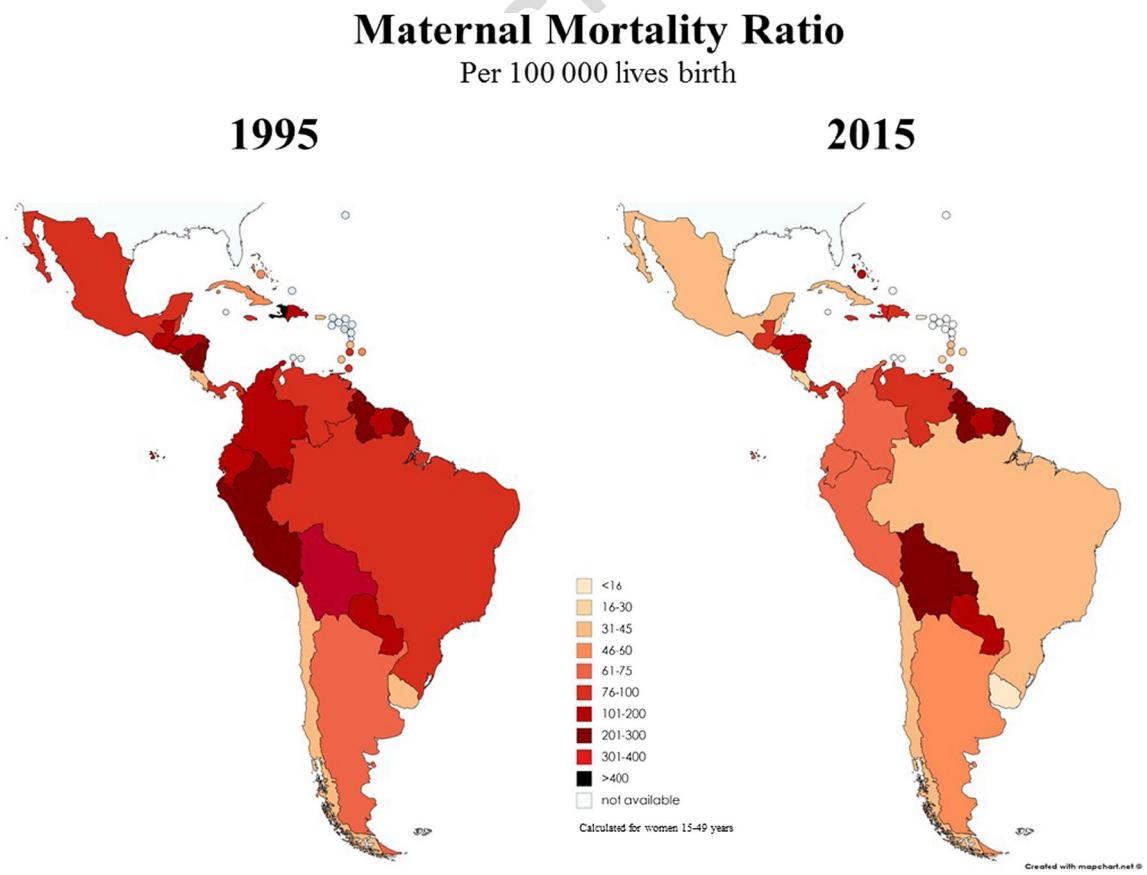


Fig. 2 Maternal mortality ratio calculated per 100,000 live births from 1995 to 2015. Compiled data from WHO, UNICEF, UNFPA, World Bank group, and United Nations Population Division, available at WWW.who.int/maternal_health

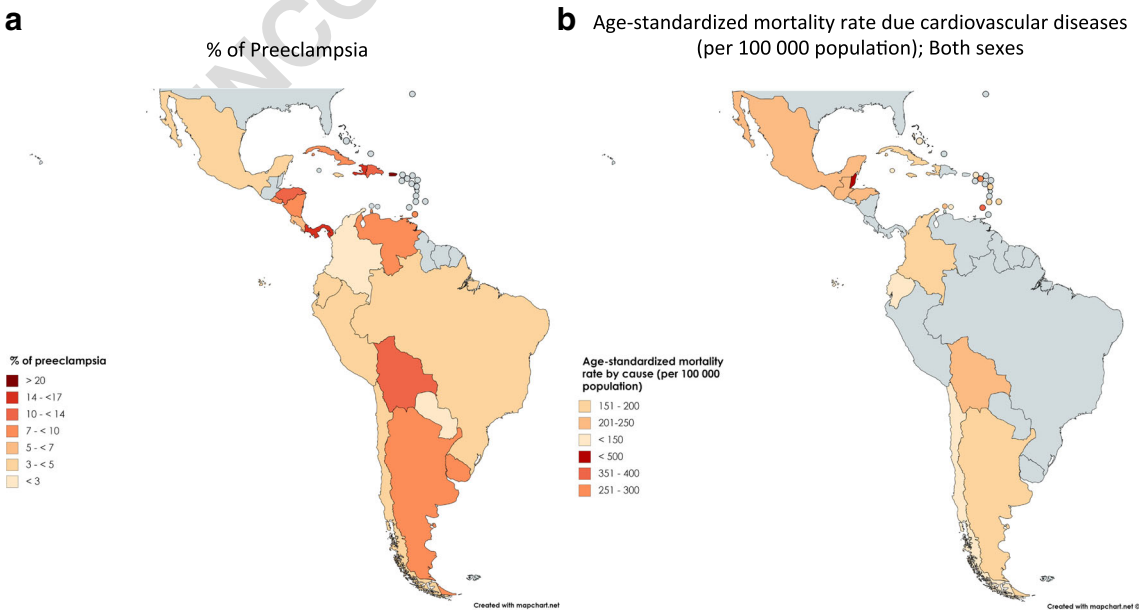
in 76,000 maternal deaths worldwide [31]. Nearly all of these maternal deaths (> 99%) occur in low- and middle-income countries [23]. Thus, preeclampsia accounts for 9% of maternal deaths in Africa and Asia and as many as 26% in the Caribbean and Latin-American countries [32]. Khan et al. [32] reported that 25.7% of maternal deaths were attributable to hypertensive disorders in Latin America and the Caribbean, reaching a total of 3800 maternal deaths in 2011 in those countries [33]. While hypertensive disorders are the second or third leading cause of maternal mortality (after hemorrhage and sepsis) in most of the world, it is the leading cause of maternal death in Latin America [34].

A meta-analysis conducted by Abalos et al. [35] found an incidence of preeclampsia and eclampsia of 3 and 0.7%, respectively, in Latin America. The authors provided estimated incidence numbers for preeclampsia in four Latin-American countries: Argentina (10.0%), Brazil (1.5%), Chile (3.4%), and Mexico (5.5%). In the case of eclampsia, the numbers are as follows: Argentina (0.4%), Brazil (0.6%), Chile (0.1%), and Mexico (0.6). In 2014, a total of 872 maternal deaths were reported in Mexico where 20.5% of these deaths were due to hypertensive disorders of pregnancy [36]. However, inadequate data in some of these countries confounds the reliability of this information. For example, our own studies demonstrated a very high prevalence of preeclampsia in Ecuador, ranging from 15 to 25%, being the hypertensive disorders the leading cause of maternal morbidity and mortality in this country [37, 38] (see Fig. 3).

Also, the incidence of preeclampsia with and without severe feature is highly dependent on the availability and quality of obstetric care during gestation. Thus, while in developed countries, the incidence of severe preeclampsia ranges from 2 to 5% [2, 39], in developing countries, severe preeclampsia and eclampsia are more common, ranging as high as 18% in some parts of Africa [2]. Therefore, in developing countries, a woman is seven times more likely to have severe preeclampsia than a woman in a developed country. Also, the lack of proper national statistics and mandatory notification polices in Latin-American countries compromises the estimation of rate of severe preeclampsia in this setting.

On another topic, Latin-American and Caribbean immigrants present increasing concern to developed countries, since they account for the highest rates of maternal mortality related to preeclampsia. This is evident in Spain, where mortality may be influenced by disparities in maternal care between the country's native population and immigrants [40].

Preeclampsia is associated with adverse fetal outcomes. It has been estimated that 12 to 25% of fetal growth restriction and small for gestational age babies are associated with preeclampsia [26, 41]. Associated complications of prematurity due to preeclampsia are neonatal deaths and serious long-term neonatal morbidity [26, 41]. It is estimated that hypertensive disorders results in 500,000 fetal/newborn deaths per year worldwide [31]. In Latin America, a study carried out in Buenos Aires, Argentina conclude that children born to gestational hypertensive pregnancies had an excess of clinical complications requiring hospitalization in the first year of life [42]. The high incidence of adverse outcome in babies born to hypertensive pregnancies was also confirmed in Chilean population [43]. These data demonstrate excess adverse perinatal



Q4 **Fig. 3** Rate of preeclampsia and cardiovascular disease in Latin-American countries. Information about rate of preeclampsia in Latin-American countries was exhaustively search from different sources (references are available under request). Also, rate of cardiovascular disease was obtained from the World Health Organization database (2012)

outcomes associated with hypertensive pregnancy outcomes are present in Latin-American countries in which the disorders are more frequent than in developed countries.

Although there are obvious deficiencies in national statistics, diagnostic criteria and care management in Latin-American countries that must be remedied our intention in this manuscript is to emphasize that progress also requires better understanding pathophysiology of preeclampsia in these countries. Potentially, unique features of preeclampsia have not been addressed. Evidence of the research deficiency is the number scientific publications (4% of all papers published worldwide in 2013 that originate in South America) or citation impact (average citation impact in South America by research field was at least 20% lower than the world average). Part of this at least is due to research funding although there are other remediable causes. One such limitation may be related to a lack of collaboration within Latin-American groups. This, despite the fact that contrary to the situation in Africa or Europe, language should not be a limitation for our countries, since Spanish is largely the official language in our countries.

Overview of Pathophysiology of Preeclampsia

The current well-accepted pathophysiology of preeclampsia indicates that this disease is characterized by impaired cytotrophoblast transformation toward extravillous trophoblasts that results in reduced invasion into the maternal vascular bed [44, 45]. This phenomenon is associated with reduced trophoblastic invasion into maternal spiral vessels, which is proposed to prevent their transformation into capacitance vessels. This, in turn, reduces maternal blood flow to the placenta and also results in high perfusion velocity in the intervillous space, generating shear stress to the trophoblast [45]. This stress damages trophoblast, which release harmful molecules including carriers of oxidative stress, inflammatory cytokines, antiangiogenic proteins, detachment and release of cell fragments, microparticles, and extracellular vesicles (EVs) [46–48]. These harmful elements enter the maternal circulation and are posited to lead maternal endothelial dysfunction. These changes also generate a vicious cycle affecting placental blood flow to lead to further release of placental materials that adversely affect maternal endothelial function [19, 49]. Not surprisingly, harmful molecules from the placenta can also reach the fetal circulation causing endothelial dysfunction. Indeed, many reports, including some from Latin-American groups [18, 50, 51], have described feto-placental endothelial dysfunction accompanying preeclamptic pregnancies.

Among other molecules released from the placenta, the soluble vascular endothelial growth factor receptor type 1 (sFlt-1) has received much attention in preeclampsia [52–61]. However, many other factors are also involved in the harmful signaling causing endothelial dysfunction in the maternal circulation. Some of the most recently identified elements are placental exosomes, containing molecules such as microRNAs that can be incorporated into the maternal cells and modify the expression of targets genes [62–64]. Most of these materials have also been proposed as biomarkers.

Study of Circulating Biomarkers for Preeclampsia in Latin-American Countries

Worldwide, the literature about biomarkers in preeclampsia is vast and, unfortunately, discrepancies in findings are often found. Part of this is due to the fact that preeclampsia is a heterogeneous syndrome. To attempt to deal with this, researchers are including more clinical data in addition to hypertension and proteinuria in the analysis. An example in a recently published study by Chen et al. [65] found specific patterns of maternal serum marker profiles according to the time of onset and fetal weight. Several reports from Latin-American countries have contributed to this field. For instance, the concentrations of antiangiogenic markers (sFlt-1 and soluble endoglin (sEng)), angiogenic placental growth factor (PIGF), and oxidative marker (oxidized low-density lipoprotein (ox-LDL)) in Colombian preeclamptic and healthy pregnant women were evaluated. In general, Colombian women with preeclampsia had lower concentrations of PIGF and higher concentrations of sEng than healthy pregnant women, without differences in ox-LDL levels. When preeclamptic women were categorized according to their gestational age, women who developed early-onset preeclampsia (before 34 weeks of gestation) had higher sFlt-1 concentrations and lower PIGF concentrations compared to healthy pregnant controls. Also, women with late-onset preeclampsia (after 34 weeks of gestation) had higher concentrations of sEng [66]. In Chile, plasma levels of sFlt-1, coagulation markers (plasminogen activator inhibitor (PAI)-1/PAI-2 ratio), and oxidative stress marker (F_2 isoprostane) were higher in women who subsequently developed preeclampsia, compared with control pregnancies [67]. Similarly, high maternal circulating sFlt-1 was found in Ecuadorian women who developed preeclampsia [68].

A multicenter study was conducted in Argentina, Colombia, Peru, India, Italy, Kenya, Switzerland, and Thailand to assess the accuracy of angiogenic biomarkers as predictors of preeclampsia in these settings. The study included 5121 pregnant women with risk factors for preeclampsia, including nulliparity, diabetes, and previous preeclampsia and chronic hypertension. Maternal serum concentrations of angiogenic markers were significantly different in women who subsequently developed preeclampsia. However, angiogenic biomarkers in the first half of pregnancy do not perform well enough to predict the later development of preeclampsia [69]. Other studies of circulating concentrations of sFlt-1, sEng, and PIGF are summarized in Table 1.

Table 1 Summary of information regarding sFlt-1, sEnd, and PGIF in population studies of preeclampsia in Latin American

Country	Gestational age	Study	Sample size	Finding in preeclampsia	Reference
Mexico	20 weeks or older	Cohort study	122 mild PE, 379 severe PE, 85 mild GH, 105 severe GH, and 75 controls	Enhanced sFlt-1 and sEng in all hypertensive disorders during pregnancy. Circulating concentration of these angiogenic factors may be useful to assess the severity of GH and PE and adverse outcome.	[70]
Brazil	Placenta	Case-control	40 early PE, 80 late PE, and 20 controls	sFlt-1 level is increased in placentas from women with early-onset of PE.	[71]
Ecuador	Early 18–25 weeks and late 28–32 weeks	Case-control	34 PE, 26 FGR, 14 PE and FGR, and 272 controls	Higher sFlt-1/PIGF ratio in PE women	[68]
Spain (multicenter)	20, 24, and 28 weeks	Prospective	78 PE and 651 controls	Higher sFlt-1/ PIGF ratio in PE women, which may improve prediction of early-onset of PE	[72]
Spain (multicenter)	11–18 weeks	Longitudinal study	22 early PE, 22 late PE, 18 GH, and 182 pregnant women with risk factors for PE	Higher sFlt-1 and lower PIGF levels in PE women. Maternal serum level of PIGF was a useful marker from the first trimester onward, while the level of sFlt-1 was likely to have a predictive value from the second trimester onward.	[73]
Argentina, Colombia, Peru, India, Italy, Kenya, Switzerland, and Thailand	Early 23–27 weeks and late 32–35 weeks	Prospective	198 PE from 5121 pregnant women with risk factors for PE	Serum concentrations of sFlt-1, PIGF, and sEng levels were enhanced in women who developed PE. However, angiogenic biomarkers in first half of pregnancy did not perform well as a predictor to later development of PE.	[69]
Brazil	20–37 weeks	Case-control	34 early PE, 26 late PE, and 60 controls	sEng is increased in the plasma from PE women.	[74]
Haiti	After 34 weeks, predelivery	Case-control	35 PE and 43 controls	Increased sFlt-1 and lower PIGF levels in PE women	[75]
Spain	8–11 weeks	Case-control	28 early PE, 84 late PE, and 84 controls.	Increased sFlt-1 and lower PIGF levels in PE women	[76]
Multicenter including Argentina, Chile, and Peru	24–37 weeks	Cohort study	500 women with clinical suspicion of, but not manifest PE or HELLP syndrome	The ratio between sFlt-1 and PIGF may be used to predict preeclampsia.	[77].
Multicenter including Spain and Germany	Early 24 weeks and late 33–39 weeks	Case-control	105 PE or HELLP and controls	Higher sFlt-1/PIGF ratio in PE/HELLP women before 34 weeks of pregnancy	[78]
Mexico	20–36 weeks	Case-control within a cohort study	37 PE and 29 controls	Higher sFlt-1 levels and sFlt-1/PIGF ratio, whereas lower PIGF levels in PE women	[79]
Multicenter including Colombia	At delivery	Case-control	143 PE and 143control	High CRP, TG, VLDL, sEnd. Low LDL, PlGF. No differences in ox-LDL or s-Flt-1	[66]
Colombia	Not informed	Case-control	604 PE and 691 controls	sFlt-1 was increased, and PIGF was reduced in PE. Increased PIGF levels above 75 pg/ml were found to be a protective factor for the development of PE and HELLP syndrome.	[80]
Chile	Early 6–15 weeks and midtrimester 20–25 weeks	Cohort study	62 PE and 150 controls	PIGF decreases, whereas sEng increases, both in early and midtrimester of preeclamptic pregnancies, suggesting that the PIGF/sEng ratio might work as an excellent predictive marker of early-onset preeclampsia.	[81].
Ecuador	At delivery	Case-control	29 PE and 29 controls	Higher plasma sFlt-1 and sEng and lower IL-8	[82]

CRP C-reactive protein, *FGR* fetal growth restriction, *GH* gestational hypertension, *HELLP* hemolysis, elevated liver enzymes, and low platelets syndrome, *LDL* low-density lipoprotein, *ox-LDL* oxidized low-density lipoprotein, *PE* preeclampsia, *PIGF* placental growth factor, *sEng* soluble endoglin, *sFlt-1* soluble fms-like tyrosine kinase 1, *TG* triglycerides, *VLDL* very low-density lipoprotein

Hence, for the particular topic of angiogenic factors, studies currently conducted in Latin America validate the findings observed around the world. However, investigators have not been particularly innovative in relating changes to unique features of Latin America or Latin-American women, such as cultural differences, nutritional habits, or genetic background. Other biomarkers associated with preeclampsia, evaluated in population studies conducted in Latin-American countries, are summarized in Table 2.

As a recommendation, future prospective studies of maternal serum analytes should include more clinical and demographic relevant to the Latin-American population. Concentrations should be determined throughout pregnancy and in the post-partum period with attention not only to the risk for preeclampsia but also to the relationship of these markers to the long-term impact on the cardiovascular health of women. Also, since preeclampsia rate is higher in Latin-American countries than developed countries, we may expect the existence of local particularities regarding pathophysiology, and perhaps, biomarkers. Therefore, we should not only test biomarkers used in developed countries but also look for novel markers ones that might be more applicable in Latin-American countries. An example can be the application of the Preeclampsia Integrated Estimate of RiSk (fullPIERS) model, which uses maternal clinical parameters and biomarkers normally used for preeclampsia diagnosis [98] to predict maternal complications in Brazilian pregnant women [99]. The use of this predictive tool may provide important diagnostic value to predict complications in preeclamptic patients but studies are required to validate this tool in other countries of Latin America.

Also, taking advantage of what have been found in epidemiological studies worldwide, preeclampsia should not be considered not only just a pregnancy complication but also a risk factor for cardiovascular disease in both mother and babies. As detailed in the next section, only few studies, mostly as part of collaborative network, have addressed this point.

Cardiovascular Diseases in Women Who Had Preeclampsia

Many of the risk factors for preeclampsia are also risk factors for later life cardiovascular disease suggesting that the increased risk of cardiovascular disease in women with preeclampsia is due to shared risk factors [25]. Nonetheless, preeclampsia is considered an independent risk factor [100] for cardiovascular disease (CVD) for both mother and her child (see below) during adulthood [12, 101–103]. Information in Latin America about this issue is limited, and we found only a few studies based in Chile [104, 105] and Brazil [106–109], Uruguay [110] and Colombia [111]. Therefore, we comment primarily on the international literature, and where possible we will highlight what is known from studies based in Latin America.

All women who have had preeclampsia exhibit at least a 2-fold increased risk of stroke cardiovascular disease and death [9, 112]. However, if preeclampsia occurs before 34 weeks gestation, death due to ischemic heart disease is increased eight times compared with controls [12]. Indeed, the American Heart Association (AHA) has included preeclampsia as a risk factor for future CVD with the recommendation to obtain a history of preeclampsia and to improve lifestyle behaviors of women with such a history [11, 101]. In Latin America, preeclamptic women from northwest of Brazil, evaluated 5 years after delivery, showed increased cardiovascular risk, and this may be related to the presence of metabolic syndrome [106, 107]. Remarkably, this group of women was unaware of their cardiovascular risk factor and furthermore reported difficulties accessing primary health care [106]. Similarly, when patients from southeast of Brazil were studied 1 year of the occurrence of preeclampsia, 41% of them displayed an increased 30-year global cardiovascular risk score. Myocardial hypertrophy was found in 29% of these women associated with obesity and increased abdominal circumference. Elevated carotid intima-medial thickness was found in 27% of the subjects, which positively correlated with overall risk as well as with myocardial hypertrophy [108]. In Colombia, Serrano-Diaz et al. [111] reported that women who had preeclampsia exhibited high diastolic blood pressure and hypercholesterolemia 2 years after delivery. Thus, studies based in Latin America also confirm coexistence of cardiovascular risk factors in women who had preeclampsia.

Imaging is an effective way to clinically follow women who had hypertensive disorders during pregnancy to assess vascular dysfunction. Women who developed preeclampsia displayed increased carotid intima-media thickness (i.e., wall thickness) measured 3 months postpartum [113], and this changed persisted 12–24 months postpartum [112]. In agreement with these findings, in Chile, a study including 217 women (average age 60 years), who presented coronary artery disease, reported that this condition presents earlier and was more severe, in women with a previous history of hypertension in pregnancy than in women with a previous normotensive pregnancy [104]. Twenty-eight percent of women who had history of hypertension in pregnancy also had coronary stenosis 10 years after delivery, compared with 22% of normotensive women ($P = 0.03$). They also reported that the odd ratio for coronary artery disease was non-significant when previous history of hypertension in pregnancy was considered in a multivariate analysis. This last finding may not only underscore the impact of association but also might be explained by reduced sample size. Contrarily, other reports found that carotid wall thickness was not observed after 4 [114] or 10 years post-partum [115], possibly due a transient adaptive response of the vasculature.

Table 2 Summary of information regarding other biomarkers found in population studies of preeclampsia in Latin American

Country	Biomarker	Gestational age	Study	Sample size	Finding in preeclampsia	Reference
Brazil	Adenosine deaminase (ADA)	34–35 weeks	Prospective	60 PE, 30 controls, and 20 non-pregnant	Elevated ADA level, IL-1β, TNF-α, and NF-κb	[83]
Colombia	Adipsin	Early 11.5–12.5 weeks, middle 24.1–24.6 weeks, late 34.2–35.2 weeks	Case-control	18 PE and 54 controls	Adipsin is elevated in PE women.	[84]
Brazil	Brain-derived neurotrophic factor (BDNF)	20–38 weeks	Case-control	38 PE and 20 controls	Lower BDNF plasma and cross-talk between BDNF and anexin-1	[85]
Ecuador	High sensitive c-reactive protein (hsCRP)	16–40 weeks	Prospective	24 PE and 183 controls	High sensitive hsCRP are augmented during preeclampsia.	[86]
Mexico	Cystatin C and Clusterin	12, 16, and 20 weeks	Cohort study	15 PE and 45 controls	Urinary cystein C and clusterin showed predictive value for PE development.	[87]
Argentina	Endocannabinoid system	At delivery Placenta	Case-control	14 PE and 14 controls	*N*-arachidonoyl phosphatidylethanolamine phospholipase D (NAPE-PLD) expression was increased, whereas fatty acid amide hydrolase (FAAH) was decreased, in PE. There were no differences in cannabinoid receptor 1 (CB1).	[88]
Chile	Glucose tolerance tests (OGTT)	22–25 weeks	Retrospective	84 PE and 1690 controls	High 2-h glucose during the second trimester of pregnancy in women who subsequently developed PE, between 35 and 37 weeks of gestation.	[89]
Mexico	Matrix metalloproteinases (MMP)	20 weeks or older	Cohort study	17 women predicted to develop PE and 48 controls	Urinary MMP-2 was increased in PE, generating an increased risk for PE development of up to 20 times.	[90]
Brazil		20 weeks and 12 weeks after delivery	Case-control	130 PE, 130 GH, and 130 controls	Plasma MMP-2 and TIMP-2 are enhanced in PE women.	[91]
Colombia	Meteorin (METRN)	Early 11.6–12.6 weeks, middle 24.2–24.6 weeks, later 34.1–35.1 weeks	Prospective cohort study	16 mild PE, 37 controls, and 20 healthy non-pregnants	METRN levels were lower only in early pregnancy in PE women.	[92]
Chile	2-Methoxyestradiol (2-ME)	11 to 14 weeks	Cohort study	13PE and 72 controls	Lower plasma concentrations of 2-ME during early pregnancy in patients who subsequently develop PE.	[93]
Paraguay	Podocalyxin	21–42 weeks	Prospective	25 PE and 38 controls	Higher levels of urinary podocalyxin, which was normalized after delivery.	[94]
Argentina	$Na^{(+)}/H^{(+)}$ exchanger isoform 3 (NHE-3)	At delivery Placenta	Case-control	10 PE and 10 controls	NHE-3 expression is decreased in PE women.	[95]
Chile	Thiobarbituric acid-reactive substances (TBARS)	At the moment of diagnosis and 30 and 120 days after delivery	Case-control	19 moderate PE, 25 severe PE, and 30 controls	High levels of TBARS and lower levels of total antioxidant capacity and enzymatic antioxidants in mother and newborns.	[96]
Colombia	Tissue factor (F3) and thrombomodulin (THBD)	At delivery Placenta	Case-control	16 PE and 19 controls	Increased placental levels of F3 and THBD along with infarction and hyperplasia of syncytiotrophoblast	[97]

2-ME 2-methoxyestradiol, *ADA* adenosine deaminase, *BDNF* brain-derived neurotrophic factor, *FAAH* fatty acid amide hydrolase, *GH* gestational hypertension, *hsCRP* high sensitive c-reactive protein, *IL-1β* interleukin 1 beta, *METRN* meteorin, *MMP* matrix metalloproteinases, *NAPE-PLD N*-arachidonoyl phosphatidylethanolamine phospholipase D, *NF-κb* nuclear factor kappa b, *NHE-3* $Na^{(+)}/H^{(+)}$ exchanger isoform 3, *OGTT* glucose tolerance tests, *PE* preeclampsia, *TBARS* thiobarbituric acid-reactive substances, *THBD* tissue factor (F3) and thrombomodulin, *TNF-α* tumor necrosis factor alpha

Other vascular indexes can also predict maternal outcome. For example, the augmentation index (AI) and pulse wave velocity (PWV), which are related to elasticity of the arterial wall, are commonly used to assess arterial stiffness. Patients diagnosed with early-onset preeclampsia displayed higher AI and PWV after delivery [116] and were also more likely to develop the metabolic syndrome [117] than controls. Indeed, augmented AI and PWV may still be observed 1 year after preeclampsia [118], reinforcing the concept that endothelial dysfunction is not totally restored after delivery. Consistent with this, although there was no follow-up, in a study in Uruguay, Torrado et al. using flow mediated dilation (FMD), low-flow-mediated constriction (L-FMC), and hyperemic-related changes in carotid-radial pulse wave velocity (PWVcr) demonstrated increased arterial stiffness in women with preeclampsia [110]. In agreement with these results, in Brazil, Henriques et al. [109] also found that 15 years after delivery, women who had hypertension in pregnancy presented impaired FMD in at a rate at least four times higher than women without history of hypertension. Therefore, imaging analysis confirms vascular dysfunction (mainly endothelial dysfunction) in Latin-American women with prior preeclampsia.

A meta-analysis including data from 37 reports, including Latin-American studies, revealed that younger women (< 40 years) with prior preeclampsia display a more pronounced endothelial dysfunction at least 3 months post partum, than older women (> 40 years) [119]. Nevertheless, no association between carotid intima-media thickness and occurrence of preeclampsia was found in young women at 20 and 30 years old [120]. Also, previous history of preeclampsia was not associated with impaired FMD or increased carotid intima-media thickness 10 years after pregnancy in previously healthy women; although, preeclampsia was associated with increased circulating markers of endothelial dysfunction such as sFlt-1 [115]. Despite these last evidences, studies indicate the specific impact of preeclampsia on CVD risk.

In an attempt to understand mechanisms for these charges, it was found that women with preeclampsia exhibited elevated blood pressure, insulin resistance, and tumor necrosis factor alpha (TNF-α) compared with women with prior normotensive pregnancies [100]. Additionally, there was a positive correlation between sFlt-1 concentration and intimal thickness and intima-medial ratio in preeclamptic women 1 year after delivery [121], demonstrating a relation between angiogenic factors and changes in vascular structure.

Additional findings relating cardiovascular disease in women with previous preeclampsia from Latin-American countries are summarized in Table 3. Findings from these studies are similar to those observed worldwide. In summary, previously preeclamptic women display findings associated with increased cardiovascular risks. These include elevated wave reflections, augmented carotid arterial stiffness, and chronic hypertension. These women also develop peripheral arterial disease and coronary disease at a younger age. The few studies from Latin-American countries usually are compromised by small sample size. Attention to these studies worldwide is limited by the fact that most are in Spanish or Portuguese. Latin-American investigators are again encouraged to initiate collaborative efforts in our region.

Cardiovascular disease as a major health issue worldwide has received much more attention than pregnancy hypertension with much more epidemiological data. We have illustrated the relationship between these conditions in Fig. 3 [35, 124]. However, this relationship is not appreciated in Latin America and we will not move forward in this area until data on hypertension in pregnancy is accurately registered and reported in our region.

Other Vascular Complications in Women Who Had Preeclampsia

Preeclamptic women display cerebral white matter lesions 3 to 6 years after a preeclamptic pregnancy, which correspond to the location of occipitoparietal edema, observed in reversible encephalopathy syndrome [125–127]. White matter lesions are independently associated with current hypertension or with a history of early-onset preeclampsia [127]. Therefore, hypertensive disorders during pregnancy might be considered an important risk marker for early cerebrovascular damage. These findings are supported by a meta-analysis demonstrating that women with previous history of hypertensive disorders during pregnancy displayed increased risk to develop cerebrovascular disease [128]. More recently, women who had preeclampsia had significantly reduced total gray matter volume and more white matter lesions in temporal lobe compared to healthy controls 5–15 years after the index pregnancy [129]. Another neurological implication of preeclampsia is the impaired cardiovascular autonomic regulation, which begins during pregnancy and may persist after delivery. We refer the reader to a review and references recently published by Logue and colleagues [130].

Although no information was found about preeclampsia and long-term neurological complication in Latin-American countries, we found information about eye function. In particular, persistent vasodilation and hyperperfusion of the orbital area were found in ophthalmic arteries 90 days after delivery in preeclamptic women from Minas Gerais, Brazil [131]. This information is related with reduced vision-related quality of life reported after 10 years of preeclamptic pregnancy, occurring simultaneously with cerebral white matter lesions reported by Wiegman and colleagues in the Netherlands [132]. These findings demonstrate that vision impairment after

Table 3 Summary of Latin-American and Spain evidences about cardiovascular disease in women who had preeclampsia

Country	Study	Sample size	Finding in preeclampsia	Reference
Uruguay	Case-control	7PE, 13 NP, 6 non-proteinuric GH, 32 non-pregnant	Elevated aortic blood pressure and wave reflections, as well as augmented elastic arteries stiffness in women with preeclampsia	[110]
Colombia	Cohort study	106 primiparous women	Changes in peripheral arterial disease (PAD) and cardiovascular risk-associated biomarkers became high 2 years after delivery in women who had PE	[111]
Chile	Case-control study	217 women who required coronary angiography	Women with HPs have earlier coronary disease, probably related to intermediate cardiovascular risks that have a gestational expression	[104]
Spain	Survey study	476 GH and 226 NP	Women with GH had the highest incidence of subsequent hypertension. Women with PE have a tending risk for developing hypertension. By contrast, women with eclampsia do not.	[122]
Brazil	Prospective case control study	242 women, 30 PE, 4 GH, 2 had superimposed hypertension, and 192 NP	Previous history of PE increases the risk of early onset of chronic hypertension.	[123]

GH gestational hypertension, *PE* preeclampsia, *NP* normal pregnancy

hypertensive disorders during pregnancy may constitute a consequence of both alterations in local vasculature and changes in the central nervous system.

Preeclampsia also is associated with an increased risk of renal disease in later life [133]. There is a lack of information about preeclampsia and long-term kidney function in Latin-American countries. In Colombia, Henao and colleagues found alteration in the membrane distribution of podocin and CD2AP in podocytes when stimulated with sera from women with preeclampsia [134]. Because of the lack of information from Latin America, our comments are limited to information from other parts of the world. Women dying from preeclampsia manifest prominent, characteristic glomerular lesions, along with a significant increase in intraglomerular cell proliferation and activated parietal epithelial cells [135]. Also, persistent urinary podocyte loss after preeclamptic pregnancies has been found, even when angiogenic markers are unchanged [136]. Thus, this feature may constitute an important marker of ongoing, subclinical renal injury. This is particularly relevant, since findings with another marker of injury, microalbuminuria, are controversial in formerly preeclamptic women. While earlier studies demonstrated a high risk of microalbuminuria after a preeclamptic pregnancy [137–141], a recent population-based study did not confirm this finding [142]. Also, it was found that previous preeclampsia does not seem to be a risk marker for progression to end-stage renal disease [143]. Then, controversy in this field reinforces the necessity of further studies evaluating kidney injury after preeclampsia.

On the other hand, Bellamy et al. [144] performed a systematic review and meta-analysis to quantify the risk of future cardiovascular disease, cancer, and mortality after preeclampsia finding increased risk for cardiovascular risk, but no association to any cancer was found. Unfortunately, we could not find information about this issue in studies based in Latin-American countries.

Adverse Cardiovascular Outcomes in Offspring of Preeclamptic Pregnancies

Many epidemiological studies report that children and adolescents who were exposed to preeclampsia or hypertension in pregnancy exhibit higher systolic and diastolic blood pressure compared with non-exposed children or adolescents (4 to 30 years old) [4, 5, 102, 145–148]. There is little information from Latin-American countries examining the relationship of preeclampsia with cardiovascular function in children born to women with this disorder [21, 149].

In a meta-analysis performed by Davis and colleagues, they concluded that offspring born from preeclamptic women had ~ 2 mmHg greater systolic and ~ 1.3 mmHg greater diastolic blood pressure than infants born from normotensive pregnancies [102]. However, this evidence has been questioned by a recent population study [150], which found that siblings born to mothers who had experienced both a hypertensive pregnancy and a normotensive pregnancy had similar increases in blood pressure when they reached adult life, when compared to offspring of mothers who had normal blood pressures in all pregnancies. [151].

Kajantie and coworkers [146] presented further evidence pointing to the association between preeclampsia and cardiovascular events in the offspring. The authors followed subjects born from 6410 singleton pregnancies, attended at two maternal hospitals in Helsinki, between 1934 and 1944. They evaluated the incidence of coronary disease, arterial hypertension, and stroke between 1971 and 2003. They found no differences in the incidence of coronary heart disease, but arterial hypertension more frequent in children from preeclamptic women. In addition, they also reported that the risk for stroke in subjects born from preeclamptic pregnancies was twice that of controls born from normotensive pregnancies.

Children born to preeclampsia exhibited greater relative wall thickness and smaller left ventricular end-diastolic volume than children born to normotensive pregnancy [152]. This effect could be early signs of concentric remodeling and could affect future cardiac function as well as risk of cardiovascular disease in offspring from preeclampsia.

Vascular alterations in offspring born to preeclamptic pregnancies were found in the analysis of childhood retinal arteriolar and venular calibers at the age of 6 years. Higher maternal systolic and diastolic blood pressures in women in early pregnancy were associated with retinal arteriolar narrowing in their children. Higher maternal systolic blood pressure in late pregnancy was associated with narrower retinal venular caliber in offspring. [153]. Yu et al. [154] found that at birth children born after hypertensive pregnancy had similar microvessel density in the skin to those born after a normotensive pregnancy. However, after the first three postnatal months that changed, when they found that offspring born after hypertensive pregnancy had ~ 2-fold greater reduction in total vessel density.

Offspring from preeclamptic women may have abnormal brain blood perfusion. Thus, brain structural and vascular anatomy from 7- to 10-year-old children born to preeclamptic pregnancies demonstrated increased regional volumes of cerebellum, temporal lobe, brain stem, and amygdala, while reduced cerebral vessel radii in the occipital and parietal lobes were observed [155]. Interestingly, they also found that children born to preeclamptic pregnancies exhibited reduced cerebral vessel radio in the occipital and parietal lobes, suggesting an intriguing hypothesis that vascular anatomic alterations in the population of offspring of preeclamptic pregnancies might be the underling mechanism for alteration in brain function of those children. This fact may also contribute to increased stroke risk to this young population in later life [156, 157].

Other studies have described an increased risk for metabolic and endocrine disease [147, 148], depression [158], cerebral palsy [159], poor cognitive outcome [160], or intellectual disabilities [161] in children born from preeclamptic pregnancies compared to non-exposed children. Also, preeclampsia is an independent predictor of low cognitive scores in preterm infants [162].

More recently, a study conducted by the WHO at centers around the globe, including Latin-American countries, found that the odds of "renal," "limb," and "lip/cleft/palate" malformations was increased four times in infants of mother with chronic hypertension [149]. They found an even higher risk (7.1 for limb to 8.7 for renal, and 4.3 for "neural tube/central nervous system" malformations) in children born to mothers with chronic hypertension with superimposed preeclampsia. The analysis also showed high risk for "cardiac" (2.3-fold) and "other" (1.6-fold) malformations due to preeclampsia. We have summarized findings about cardiovascular and non-cardiovascular diseases in children born to preeclamptic women in Table 4.

Despite the high incidence of preeclampsia in Latin America, there are insufficient studies to elucidate the long-term effects of this disease in the adulthood of the offspring. In one study, Jayet et al. [21] evaluated 48 children of pregnant women with preeclampsia and compared them with 90 children born of normal pregnancies, who have lived all their lives at 3600 m above sea level, in La Paz, Bolivia. The average age of the children was 14 years. They found that the systolic gradient between atrium and ventricle was higher among children from preeclamptic mothers (32.1 ± 5.6 vs 25.3 ± 4.7 Torr), whereas vasodilatation mediated by flow was lower in this group (6.2 ± 3.5 vs 8.3 ± 1.6%). Their findings confirm that preeclampsia affects vascular functions in children born to preeclamptic pregnancies in Latin America but more information is required.

Vascular/Endothelial Dysfunction in Preeclampsia: Is it the Same in Mother and Offspring?

Several mechanisms for vascular/endothelial dysfunction have been studied since Roberts et al. proposed endothelial dysfunction as the underling alteration in preeclampsia in 1989 [16]. This concept has been expanded to include feto-placental circulation, offspring circulation, and it is suggested as one of the main mechanisms linked with future cardiovascular risk in mother and her offspring. We summarize this information in Fig. 4 and suggest excellent recent reviews on this topic [7–9, 119, 167–169]. One mechanisms extensively studied including groups based in Latin-American countries is the synthesis and action of nitric oxide (NO). Impaired synthesis and/or action is present in maternal [37, 170–173], placental [174, 175], and umbilical [19, 176] vessels of hypertensive pregnancies. Not only are functions of blood vessels impaired in preeclampsia but also angiogenesis itself [50, 177]. Currently, it is unclear whether this impaired angiogenesis or vascular dysfunction is generalized or whether this is a tissue specific-phenomenon. Interestingly, these mechanisms have been also linked with other pregnancy disorders such as gestational diabetes, intrauterine growth restriction, and preterm delivery among others.

However, a question that remains unsolved is whether vascular endothelial dysfunction is the same in mother and offspring in preeclamptic pregnancies. An excellent study by Yu et al. [154] found that offspring born after hypertensive pregnancy had a ~ 2-fold greater reduction of total vessel density in the skin. Interestingly, this phenomenon was associated with reduced in vitro vasculogenic capacity of the human umbilical vein endothelial cells of the infant at birth and was proportional to levels of antiangiogenic factors in the maternal circulation.

Q6 **Table 4** Summary evidences about cardiovascular and non-cardiovascular diseases in children born to preeclampsia

Country	Study	Sample size	Finding in preeclampsia	Reference
Denmark	Population study	1,618,481 singleton-born children	High risk of child to be hospitalized for any cause during the first 24 years of life.	[147]
Argentina	Retrospective longitudinal cohort study	351 cases		[42]
USA	Prospective study	10 singleton-born children	Reduction of cognitive, affecting working memory and oculomotor control	[163]
Australia	Prospective study	2601 participants	Small reduction in verbal abilities at age of 10 years	[164]
Australia	Prospective study	2804 women and their children	Poorer behavior	[165]
Denmark	Population study	22,264 discordant sib-pairs	High risk for respiratory diseases	[148]
Denmark	Population study	1,077,432 singleton-born children		[147]
Australia		413 cases		[159]
Finland	Cohort study	6410 cases	Increase arterial hypertension coronary disease, and stroke	[146]
Bolivia	Prospective study	138 cases	Systemic and pulmonary vascular dysfunction	[21]
Denmark	Population study	1,077,432 singleton-born children	Metabolic diseases	[147]
Finland	Retrospective longitudinal cohort study	788 cases	Later depressive symptoms	[158]
Netherlands	Population study	3748 cases	Vascular alterations	[153]
UK	Prospective study	600 participants		[154]
Australia	Prospective case-control	413 cases	Low birth weight	[159]
29 countries including Argentina, Brazil, Ecuador, Mexico, Nicaragua, Paraguay, and Peru	Population study involving five WHO regions: African, the Americas, Eastern Mediterranean, Southeast Asia and Western Pacific Region	310,401 live births	Malformations in the central nervous system, renal, limp, cardiac, lip/cleft/palate, and chromosomal	[149]
Norway	A nested case-control study	12,804 consecutive singleton deliveries	Nutritional and endocrine disease	[166]
Denmark		1,077,432 singleton-born children		[147]

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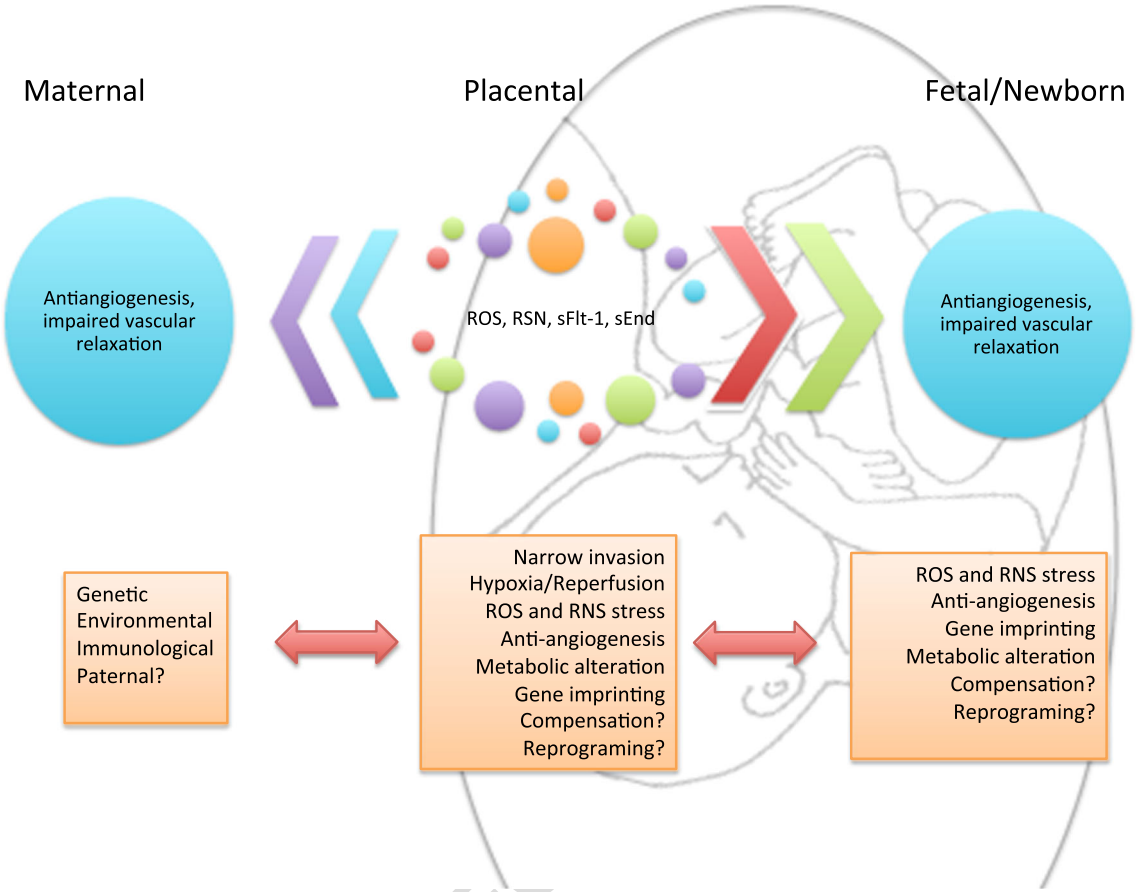

Fig. 4 Endothelial dysfunction in maternal, placental, and fetal circulation in preeclampsia. Interaction between maternal, placental, and fetal/newborn compartments. Ischemic placenta can release several signaling molecules into both maternal and fetal compartment, which have been associated with endothelial dysfunction. Endothelial dysfunction includes impaired vascular relaxation and anti-angiogenesis. Many other factors are playing a role in endothelial dysfunction present in the three compartments during preeclampsia. Lists of them are included in the boxes in the bottom of this cartoon. See details in the text

Lower concentrations of PIGF during the second trimester of pregnancy were associated with narrower childhood retinal arteriolar caliber. However, this association was not explained by maternal blood pressure but may be related by the offspring's blood pressure [178]. Similar to Yu's group work, the last study suggests that angiogenic factors from the mother may have an independent impact on fetal vascular development, at least in the eye. This last conclusion also leads to another basic question, whether impaired endothelial dysfunction is a generalized phenomenon or instead is tissue-specific. General agreement tends toward a generalized phenomenon, but more recent evidence in the brain [129, 156, 157, 163] or eye [156, 179, 180] could indicate a more selective process.

The causes of vascular dysfunction in the mother, in the placenta, and in the fetus are not well understood. But since reduction in microvascular density in offspring of preeclamptic pregnancies was predicted by in vitro alteration in the tube formation capacity of umbilical vein endothelial cells, as well as the concentration of angiogenic factors in maternal circulation around the time of birth [154], it may indicate that the offspring is responding to rather than causing vascular alterations in the mother and placenta. More investigation is needed worldwide to elucidate this issue.

Recently Described Cellular Mechanism of Endothelial Dysfunction in Preeclampsia

Many potential mechanisms are being studied to understand endothelial dysfunction in preeclampsia. The role of mitochondrial DNA (mtDNA) is suggested as a contributor to vascular dysfunction in preeclampsia. The mtDNA, which are potent immunological activators, are released as a result of cell death, and may induce vascular changes and predispose to cardiovascular disease [181]. Recent findings from experimental studies conducted in rats show that mtDNA, released from necrotic trophoblastic cells activate the immune system via Toll-like receptor 9 (TLR9), activating protein kinases (MAPK) and potentiating the release of pro-inflammatory cytokines This then results in systemic vascular dysfunction and generation of preeclampsia-like symptoms [182]. Dysfunctional mitochondria are also a powerful source of reactive oxygen species (ROS), molecules that are

intermediaries of preeclampsia. Increased ROS-mediated deleterious redox signaling may further result in maternal vascular dysfunction, as recently suggested by [183]. These ideas are supported by the fact that many preeclamptic women exhibit necrotic placentas [184] and emerging findings of elevated circulating mtDNA in preeclampsia [185].

Another example of endothelial dysfunction in preeclampsia is related to transport and catabolism of metabolic active substrates, including glucose, amino acids, or fatty acids. This is relevant since most of the energy of endothelial cells comes from glycolysis [186]. In preeclampsia, inactivation of glucose-6-phosphate dehydrogenase (G6PD), a rate-limiting enzyme in glucose metabolism, occurs in the human fetal circulation (erythrocytes and fetal endothelial cells), a phenomenon associated with the vascular dysfunction and oxidative stress [187]. Similarly, reduced transport and/or metabolism of other bioactive molecules such as adenosine or L-arginine [176], or metabolism of other sources of energy such as fatty acids [188], might also contribute to the metabolic alterations leading to endothelial dysfunction in preeclampsia.

Another obvious contribution is genetic background. Since preeclampsia is a heterogeneous disorder highly prevalent in Latin-American countries, its understanding requires population based genetic studies. Some studies have begun to look at this question in Latin America populations. For instance, genetic studies have associated single nucleotide polymorphisms (SNP) in genes encoding nitric oxide synthase with preeclampsia, but the results are not consistent in different populations. Three polymorphisms in the eNOS gene: a SNP in the promoter region, the –786T → C, a variable number of tandem repeats in intron 4, and a SNP in exon 7 (Glu298Asp) have been demonstrated in women from Latin America. Colombian women homozygous for the Asp298 allele, as well as women with the Asp298–786C-4b haplotype, were associated with preeclampsia [173]. Mayan mestizo women homozygous for the Asp298 allele demonstrated this association with preeclampsia but the haplotype -786C-4b-Asp298 was a better genetic marker in this population [189]. In Brazilian women with preeclampsia, Sandrim et al. did not find significant differences in genotype distribution of the three polymorphisms between preeclampsia and healthy women [190]. However, a more recent study in Brazilian women with preeclampsia reported that the NOS3 T-786C SNP is associated with preeclampsia and the severity of its complications [191]. Clearly, more studies are needed with consideration of the regional and genetic background of the studied population.

Epigenetic changes consisted with vascular dysfunction are present in subjects with preeclampsia. Julian et al. [192], studying a small group of Andean people (18–25 years) living in La Paz, Bolivia, found that men whose mothers had pregnancy complicated with hypertension exhibited at least six genome-wide significant methylated genomic regions (DMR) than to control subjects. Of the six DMRs, three were hypomethylated and three were hypermethylated in hypertensive pregnancies versus controls. These regions were associated with genes such has *CTHRC1* (collagen triple helix repeat containing 1), *TRIM31* (tripartite motif containing 31), *ARID1B* (AT rich interactive domain 1B), *SMOC2* (SPARC related modular calcium binding 2), *LRRIQ3* (leucine-rich repeats and IQ motif containing 3), or LINC00226 (long intergenic non-protein coding RNA 226). Several of these genes have a potential modulatory role in vascular function. Also, they found that *ARID1B* gene expression was impaired in offspring from preeclamptic pregnancies ($p = 0.025$). These studies not only confirmed that epigenetic mechanisms are involved in vascular risk in offspring from preeclamptic pregnancies but also introduced novel targets for future research.

Need for Action in Latin-American Countries

There are many cultural, sociodemographic, economic, and geographic variations in Latin-American countries that must be considered in any epidemiological analysis. Preeclampsia is a major health problem in our countries. As presented in this manuscript, consequences for mothers and their children do not end with delivery but extend into adulthood. Maternal and offspring health issues related to preeclampsia such as obesity, metabolic syndrome, and vascular related complications are of major concern in Latin-American countries. Unfortunately, information about the impact of preeclampsia on both mothers and their children is quite limited in our countries and almost exclusively focused on local communities. Thus, there is a crucial need for collaborative research efforts. These studies should broaden the search for new strategies directed to the understanding of vascular disorders of pregnancy to lead to improved health outcomes in our countries.

Knowledge derived from research in preeclampsia originates primarily from high-income countries. Also, as non-English speaking countries, Latin-American scientific papers are usually published in low impact journals and are often relegated to meta-analysis or topic review. Much data from Latin-American countries are published only in local journals without easy access to the larger scientific community. Despite information that may contribute to the field, the language limitation negatively impacts the possibility of reaching larger audiences. Statistical information on health services while used for national or local reports are not published for public access. We believe that this limitation not only affects scientists in Latin America but also may constitute a gap in science, as reported recently [193].

Moreover, differences in diagnostic and management criteria of the disease indicate the necessity of regional agreements. Such homogenization would increase the opportunities for commonality in research studies but could also lead to the development of useful clinical guidelines for the region. We

strongly believe that the limited resources currently available for basic and clinical research, as well as the inadequate communication between groups contributes to the disparate and limited information from our countries. Despite the limited resources throughout the entire Latin-American region, Brazil is the only country to spend more than 1% of its gross domestic product (GDP) on research and development (WHO recommends 2%), while the remaining Latin-American countries expend below 0.6% or probably even lower as no clear data was available [193]. Even in those Latin-American countries with better emphasis on science such as Argentina, Brazil, Chile, or Mexico, there has been only limited intraregional collaboration [193]. A quite remarkable fact observed in our countries is that the less resources investigators have, the more collaboration they establish with countries outside Latin America. We must begin to view each other as collaborators, not as competitors.

Therefore, as for the low- and middle-income countries, the benefits to establish collaborations are clear. Of great value would be the formation of collaborative networks or consortia among researchers in different countries in the region, who would consider sharing resources, including clinical information and biological samples. At the same time, temporary visits of researchers and students are necessary to facilitate the exchange of expertise and dynamic flow of information among our countries. We believe that this would promote increased scientific research efforts and the generation of valuable regional information related to hypertensive disorders of pregnancy and other adverse pregnancy outcomes.

Conclusions

The following are a few examples of important actions to implement now or in the very near future that will help us improve our knowledge and increase our research findings in the field of preeclampsia and its cardiovascular complications. We include only a few but certainly more will be required.

- Multicenter studies. Institute multicenter studies and establish a consistent diagnosis of preeclampsia (and other forms of hypertension in pregnancy). Use this mechanism to determine its short and long-term complications in mothers and their descendants in the Latin-American population. Improve the quality and number of clinical research studies with Latin-American pregnancies, attempting to find biological markers perhaps specific to this population. Development of these multicenter studies not only will generate improved data and reports compared to individual efforts but will also contribute to improved local scientific experience for conducting epidemiological, clinical and basic science studies.
- Win-win collaboration. Because participation in scientific educational programs and research projects is diverse in our countries, collaborative efforts will address this issue. Countries such as Argentina, Brazil, Mexico, and Chile, in which development of sciences has advanced more than in some other countries, will be called to support development of other groups in our region. This effort will be addressed with the required exchange visits of faculty and sharing of postgraduate programs. In addition, collaboration with international groups from developed countries is always welcomed. Fortunately, our countries have Q7 productive collaborative work with developed countries, even better that within Latin America [193]. Many advantages can be overseen from established collaborative networks in terms of potentiating each other, increase productivity, and impact of research and not lest important might increase the chance to get founding.
- Enhance the knowledge. We need to develop academic programs for clinical trainees in order to continually update their knowledge in this field and also motivate them in development of new knowledge, information, and techniques using local capacities.
- Seek local risk factors and biomarkers. As has been done in other areas, we want to identify risk factors of preeclampsia at the as early as possible. This is important, since as referenced in this manuscript, studies currently conducted in our countries usually include risk factors and biomarkers tdiscovered and ested in developed countries, which may not be the same in our population. Also, the search for local risk factors for preeclampsia should be taken into account as they impact not only the incidence but also the prognosis and management. For instance, Latin-American Study of Nutrition and Health (ELANS) reports that nearly a quarter of the population is obese, and the prevalence has increased to a greater magnitude in Mexico, Argentina, and Chile. A recent review estimated that 20–25% of Latin-American children and adolescents (0–18 years) are overweight or obese [194]. Since obesity is a well-described risk factor for hypertension, and considering the genetic background, we wonder how these diseases will impact future generations. This is one example of how a common health problem underlying preeclampsia could be one of the useful starting points for collaborative research.
- Update guidelines. Our countries have adapted guidelines originating from developed countries, most notably, American College of Obstetricians and Gynecologists (ACOG). Recommendations of ACOG were modified in 2013, but we have no information about the impact of that update in our countries. Also, local problems demonstrate the necessity for developing regional guidelines to monitor blood pressure during pregnancy, improve prenatal

health care, and improve follow-up care of mothers and infants following the onset of preeclampsia.

- Clinical guidelines. Although it was not the focus of this review, we should also consider differences in pharmacological and non-pharmacological treatment among our countries or even within countries in our region. Differences are not necessarily related to changes in the clinical decision, but rather to the availabilty of physical resources, such as infrastructure, availability of drugs, and use of generic rather than commercial presentation of drugs, among others. Nonetheless, we must seek the most efficacous approach to therapy and emphasize the importance of striving to generalize this strategy.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest relevant to this manuscript.

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Q9 References

1. Xiong X, Demianczuk NN, Saunders LD, Wang FL, Fraser WD. Impact of preeclampsia and gestational hypertension on birth weight by gestational age. Am J Epidemiol. 2002;155(3):203–9.
2. Villar J, Carroli G, Wojdyla D, Abalos E, Giordano D, Ba'aqeel H, et al. Preeclampsia, gestational hypertension and intrauterine growth restriction, related or independent conditions? Am J Obstet Gynecol. 2006;194(4):921–31. https://doi.org/10.1016/j.ajog.2005.10.813.
3. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet. 2005;365(9461):785–99.
4. Davis EF, Newton L, Lewandowski AJ, Lazdam M, Kelly BA, Kyriakou T, et al. Pre-eclampsia and offspring cardiovascular health: mechanistic insights from experimental studies. Clin Sci (Lond). 2012;123(2):53–72. https://doi.org/10.1042/CS20110627.
5. Glover V. Annual research review: prenatal stress and the origins of psychopathology: an evolutionary perspective. J Child Psychol Psychiatry. 2011;52(4):356–67. https://doi.org/10.1111/j.1469-7610.2011.02371.x.
6. Hanson MA, Gluckman PD. Developmental origins of health and disease: new insights. Basic Clin Pharmacol Toxicol. 2008;102(2):90–3. https://doi.org/10.1111/j.1742-7843.2007.00186.x.
7. Enkhmaa D, Wall D, Mehta PK, Stuart JJ, Rich-Edwards JW, Merz CN, et al. Preeclampsia and vascular function: a window to future cardiovascular disease risk. J Women's Health (Larchmt). 2016;25(3):284–91. https://doi.org/10.1089/jwh.2015.5414.
8. Kattah AG, Scantlebury DC, Agarwal S, Mielke MM, Rocca WA, Weaver AL, et al. Preeclampsia and ESRD: the role of shared risk factors. Am J Kidney Dis. 2016; https://doi.org/10.1053/j.ajkd.2016.07.034.
9. Weissgerber TL, Milic NM, Milin-Lazovic JS, Garovic VD. Impaired flow-mediated dilation before, during, and after preeclampsia: a systematic review and meta-analysis. Hypertension. 2016;67(2):415–23. https://doi.org/10.1161/HYPERTENSIONAHA.115.06554.
10. Cirillo PM, Cohn BA. Pregnancy complications and cardiovascular disease death: 50-year follow-up of the child health and development studies pregnancy cohort. Circulation. 2015;132(13):1234–42. https://doi.org/10.1161/CIRCULATIONAHA.113.003901.
11. Seely EW, Rich-Edwards J, Lui J, Nicklas JM, Saxena A, Tsigas E, et al. Risk of future cardiovascular disease in women with prior preeclampsia: a focus group study. BMC Pregnancy Childbirth. 2013;13:240. https://doi.org/10.1186/1471-2393-13-240.
12. Mongraw-Chaffin ML, Cirillo PM, Cohn BA. Preeclampsia and cardiovascular disease death: prospective evidence from the child health and development studies cohort. Hypertension. 2010;56(1):166–71. https://doi.org/10.1161/HYPERTENSIONAHA.110.150078.
13. Brunner H, Cockcroft JR, Deanfield J, Donald A, Ferrannini E, Halcox J, et al. Endothelial function and dysfunction. Part II: association with cardiovascular risk factors and diseases. A statement by the working group on endothelins and endothelial factors of the European Society of Hypertension. J Hypertens. 2005;23(2):233–46.
14. Deanfield J, Donald A, Ferri C, Giannattasio C, Halcox J, Halligan S, et al. Endothelial function and dysfunction. Part I: methodological issues for assessment in the different vascular beds: a statement by the Working Group on Endothelin and Endothelial Factors of the European Society of Hypertension. J Hypertens. 2005;23(1):7–17.
15. Roberts JM. Endothelial dysfunction in preeclampsia. Semin Reprod Endocrinol. 1998;16(1):5–15. https://doi.org/10.1055/s-2007-1016248.
16. Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA, McLaughlin MK. Preeclampsia: an endothelial cell disorder. Am J Obstet Gynecol. 1989;161(5):1200–4.
17. Rodgers GM, Taylor RN, Roberts JM. Preeclampsia is associated with a serum factor cytotoxic to human endothelial cells. Am J Obstet Gynecol. 1988;159(4):908–14.
18. Wadsack C, Desoye G, Hiden U. The feto-placental endothelium in pregnancy pathologies. Wien Med Wochenschr. 2012;162(9–10):220–4. https://doi.org/10.1007/s10354-012-0075-2.
19. Sobrevia LG-G,E, Westermeier F, Salomón C, Arroyo P, Palacios E, Bugueño K, et al. Fetoplacental vascular pathophysiology in preeclampsia. In: Sobrevia L, editor. Recent research developments in physiology. India: Research Signpost; 2012. p. 105–58.
20. Kvehaugen AS, Dechend R, Ramstad HB, Troisi R, Fugelseth D, Staff AC. Endothelial function and circulating biomarkers are disturbed in women and children after preeclampsia. Hypertension. 2011;58(1):63–9. https://doi.org/10.1161/HYPERTENSIONAHA.111.172387.

21. Jayet PY, Rimoldi SF, Stuber T, Salmon CS, Hutter D, Rexhaj E, et al. Pulmonary and systemic vascular dysfunction in young offspring of mothers with preeclampsia. Circulation. 2010;122(5):488–94. https://doi.org/10.1161/CIRCULATIONAHA.110.941203.
22. Lazdam M, de la Horra A, Pitcher A, Mannie Z, Diesch J, Trevitt C, et al. Elevated blood pressure in offspring born premature to hypertensive pregnancy: is endothelial dysfunction the underlying vascular mechanism? Hypertension. 2010;56(1):159–65. https://doi.org/10.1161/HYPERTENSIONAHA.110.150235.
23. Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol. 2009;33(3):130–7. https://doi.org/10.1053/j.semperi.2009.02.010.
24. Sliwa K, Bohm M. Incidence and prevalence of pregnancy-related heart disease. Cardiovasc Res. 2014;101(4):554–60. https://doi.org/10.1093/cvr/cvu012.
25. Fraser A, Nelson SM, Macdonald-Wallis C, Cherry L, Butler E, Sattar N, et al. 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(11):1367–80. https://doi.org/10.1161/CIRCULATIONAHA.111.044784.
26. Wallis AB, Saftlas AF, Hsia J, Atrash HK. Secular trends in the rates of preeclampsia, eclampsia, and gestational hypertension, United States, 1987-2004. Am J Hypertens. 2008;21(5):521–6. https://doi.org/10.1038/ajh.2008.20.
27. Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol. 2000;183(1):S1-S22.
28. American College of O, Gynecologists, Task Force on Hypertension in P. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122(5):1122–31. https://doi.org/10.1097/01.AOG.0000437382.03963.88.
29. WHO. Maternal mortality. Data by WHO region. 2016. http://apps.who.int/gho/data/view.main.1370?lang=en. 2016.
30. Roost M, Altamirano VC, Liljestrand J, Essen B. Priorities in emergency obstetric care in Bolivia—maternal mortality and near-miss morbidity in metropolitan La Paz. BJOG. 2009;116(9):1210–7. https://doi.org/10.1111/j.1471-0528.2009.02209.x.
31. Khowaja AR, Mitton C, Bryan S, Magee LA, Bhutta ZA, von Dadelszen P. Economic evaluation of community level interventions for pre-eclampsia (CLIP) in South Asian and African countries: a study protocol. Implement Sci. 2015;10(1):76. https://doi.org/10.1186/s13012-015-0266-5.
32. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006;367(9516):1066–74. https://doi.org/10.1016/S0140-6736(06)68397-9.
33. Hutcheon JA, Lisonkova S, Joseph KS. Epidemiology of pre-eclampsia and the other hypertensive disorders of pregnancy. Best Pract Res Clin Obstet Gynaecol. 2011;25(4):391–403. https://doi.org/10.1016/j.bpobgyn.2011.01.006.
34. Foundation P. Preeclampsia: a decade of perspective, building a global call to action., Melbourne, Florida. 2010.
35. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. Eur J Obstet Gynecol Reprod Biol. 2013;170(1):1–7. https://doi.org/10.1016/j.ejogrb.2013.05.005.
36. México. SdSCNdEdGySR. Prevención, diagnóstico y manejo de la preeclampsia/eclampsia. Lineamiento Técnico. Mexico 2007.
37. Teran E, Escudero C, Vivero S, Molina G, Calle A. NO in early pregnancy and development of preeclampsia. Hypertension. 2006;47(4):e17. https://doi.org/10.1161/01.HYP.0000205226.01641.fe.
38. Teran E, Hernandez I, Nieto B, Tavara R, Ocampo JE, Calle A. Coenzyme Q10 supplementation during pregnancy reduces the risk of pre-eclampsia. Int J Gynaecol Obstet. 2009;105(1):43–5. https://doi.org/10.1016/j.ijgo.2008.11.033.
39. Ronsmans C, Graham WJ. Lancet maternal survival series steering g. Maternal mortality: who, when, where, and why. Lancet. 2006;368(9542):1189–200. https://doi.org/10.1016/S0140-6736(06)69380-X.
40. Urquia ML, Glazier RH, Gagnon AJ, Mortensen LH, Nybo Andersen AM, Janevic T, et al. Disparities in pre-eclampsia and eclampsia among immigrant women giving birth in six industrialised countries. BJOG. 2014;121(12):1492–500. https://doi.org/10.1111/1471-0528.12758.
41. Porreco RP, Barkey R. Peripartum intensive care. J Matern Fetal Neonatal Med. 2010;23(10):1136–8. https://doi.org/10.3109/14767058.2010.490890.
42. Corominas AI BS, Palermo M, Maskin B, Damiano AE. Maternal hypertensive environment and postnatal susceptibility to disease. Placenta. 2013;34(A32).
43. Bertoglia PRA, Navarrete P, Castro L, Acurio J, Escudero C. Resultados clínicos y perinatales de los embarazos con hipertensión arterial en un hospital de referencia de la VIII región de Chile. Rev Chil Obstet Ginecol. 2010;75(3):162–71.
44. Burton GJ, Charnock-Jones DS, Jauniaux E. Regulation of vascular growth and function in the human placenta. Reproduction. 2009;138(6):895–902. https://doi.org/10.1530/REP-09-0092.
45. Burton GJ, Woods AW, Jauniaux E, Kingdom JC. Rheological and physiological consequences of conversion of the maternal spiral arteries for uteroplacental blood flow during human pregnancy. Placenta. 2009;30(6):473–82.
46. Redman CW, Sargent IL. Latest advances in understanding pre-eclampsia. Science. 2005;308(5728):1592–4. https://doi.org/10.1126/science.1111726.
47. Redman CW, Sargent IL. Placental debris, oxidative stress and pre-eclampsia. Placenta. 2000;21(7):597–602. https://doi.org/10.1053/plac.2000.0560.
48. Tannetta DS, Dragovic RA, Gardiner C, Redman CW, Sargent IL. Characterisation of syncytiotrophoblast vesicles in normal pregnancy and pre-eclampsia: expression of flt-1 and endoglin. PLoS One. 2013;8(2):e56754. https://doi.org/10.1371/journal.pone.0056754.
49. Roberts JM, Escudero C. The placenta in preeclampsia. Hypertens Pregnancy. 2012;2(2):72–83.
50. Escudero C, Roberts JM, Myatt L, Feoktistov I. Impaired adenosine-mediated angiogenesis in preeclampsia: potential implications for fetal programming. Front Pharmacol. 2014;5:134. https://doi.org/10.3389/fphar.2014.00134.
51. Germain SJ, Sacks GP, Sooranna SR, Sargent IL, Redman CW. Systemic inflammatory priming in normal pregnancy and pre-eclampsia: the role of circulating syncytiotrophoblast microparticles. J Immunol. 2007;178(9):5949–56.
52. Agarwal I, Karumanchi SA. Preeclampsia and the anti-angiogenic state. Pregnancy Hypertens. 2011;1(1):17–21. https://doi.org/10.1016/j.preghy.2010.10.007.
53. Levine RJ, Karumanchi SA. Circulating angiogenic factors in pre-eclampsia. Clin Obstet Gynecol. 2005;48(2):372–86.
54. Levine RJ, Lam C, Qian C, Yu KF, Maynard SE, Sachs BP, et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. N Engl J Med. 2006;355(10):992–1005. https://doi.org/10.1056/NEJMoa055352.
55. Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, et al. Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med. 2004;350(7):672–83. https://doi.org/10.1056/NEJMoa031884.

56. Levine RJ, Qian C, Maynard SE, Yu KF, Epstein FH, Karumanchi SA. Serum sFlt1 concentration during preeclampsia and mid trimester blood pressure in healthy nulliparous women. Am J Obstet Gynecol. 2006;194(4):1034–41. https://doi.org/10.1016/j.ajog.2005.10.192.
57. Levine RJ, Thadhani R, Qian C, Lam C, Lim KH, Yu KF, et al. Urinary placental growth factor and risk of preeclampsia. JAMA. 2005;293(1):77–85. https://doi.org/10.1001/jama.293.1.77.
58. Maynard SE, Karumanchi SA. Angiogenic factors and preeclampsia. Semin Nephrol. 2011;31(1):33–46. https://doi.org/10.1016/j.semnephrol.2010.10.004.
59. Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest. 2003;111(5):649–58. https://doi.org/10.1172/JCI17189.
60. Silasi M, Cohen B, Karumanchi SA, Rana S. Abnormal placentation, angiogenic factors, and the pathogenesis of preeclampsia. Obstet Gynecol Clin N Am. 2010;37(2):239–53. https://doi.org/10.1016/j.ogc.2010.02.013.
61. Sunderji S, Gaziano E, Wothe D, Rogers LC, Sibai B, Karumanchi SA, et al. Automated assays for sVEGF R1 and PlGF as an aid in the diagnosis of preterm preeclampsia: a prospective clinical study. Am J Obstet Gynecol. 2010;202(1):40 e1–7. https://doi.org/10.1016/j.ajog.2009.07.025.
62. Chen DB, Wang W. Human placental microRNAs and preeclampsia. Biol Reprod. 2013;88(5):130. https://doi.org/10.1095/biolreprod.113.107805.
63. Fu G, Brkic J, Hayder H, Peng C. MicroRNAs in human placental development and pregnancy complications. Int J Mol Sci. 2013;14(3):5519–44. https://doi.org/10.3390/ijms14035519.
64. Escudero CA, Herlitz K, Troncoso F, Acurio J, Aguayo C, Roberts JM, et al. Role of extracellular vesicles and microRNAs on dysfunctional angiogenesis during preeclamptic pregnancies. Front Physiol. 2016;7:98. https://doi.org/10.3389/fphys.2016.00098.
65. Cheng PJ, Huang SY, Su SY, Hsiao CH, Peng HH, Duan T. Prognostic value of cardiovascular disease risk factors measured in the first-trimester on the severity of preeclampsia. Medicine (Baltimore). 2016;95(5):e2653. https://doi.org/10.1097/MD.0000000000002653.
66. Reyes LM, Garcia RG, Ruiz SL, Broadhurst D, Aroca G, Davidge ST, et al. Angiogenic imbalance and plasma lipid alterations in women with preeclampsia from a developing country. Growth Factors. 2012;30(3):158–66. https://doi.org/10.3109/08977194.2012.674035.
67. Parra M, Rodrigo R, Barja P, Bosco C, Fernandez V, Munoz H, et al. Screening test for preeclampsia through assessment of uteroplacental blood flow and biochemical markers of oxidative stress and endothelial dysfunction. Am J Obstet Gynecol. 2005;193(4):1486–91. https://doi.org/10.1016/j.ajog.2005.02.109.
68. Kienast C, Moya W, Rodriguez O, Jijon A, Geipel A. Predictive value of angiogenic factors, clinical risk factors and uterine artery Doppler for pre-eclampsia and fetal growth restriction in second and third trimester pregnancies in an Ecuadorian population. J Matern Fetal Neonatal Med. 2016;29(4):537–43. https://doi.org/10.3109/14767058.2015.1012063.
69. Widmer M, Cuesta C, Khan KS, Conde-Agudelo A, Carroli G, Fusey S, et al. Accuracy of angiogenic biomarkers at 20 weeks' gestation in predicting the risk of pre-eclampsia: a WHO multicentre study. Pregnancy Hypertens. 2015;5(4):330–8. https://doi.org/10.1016/j.preghy.2015.09.004.
70. Leanos-Miranda A, Mendez-Aguilar F, Ramirez-Valenzuela KL, Serrano-Rodriguez M, Berumen-Lechuga G, Molina-Perez CJ, et al. Circulating angiogenic factors are related to the severity of gestational hypertension and preeclampsia, and their adverse outcomes. Medicine (Baltimore). 2017;96(4):e6005. https://doi.org/10.1097/MD.0000000000006005.
71. Weel IC, Baergen RN, Romao-Veiga M, Borges VT, Ribeiro VR, Witkin SS, et al. Association between placental lesions, cytokines and angiogenic factors in pregnant women with preeclampsia. PLoS One. 2016;11(6):e0157584. https://doi.org/10.1371/journal.pone.0157584.
72. Perales A, Delgado JL, De La Calle M, Garcia-Hernandez JA, Escudero AI, Campillos JM, et al. sFlt-1/PlGF for early-onset pre-eclampsia prediction: STEPS (study of early pre-eclampsia in Spain). Ultrasound Obstet Gynecol. 2016; https://doi.org/10.1002/uog.17373.
73. Khalil A, Maiz N, Garcia-Mandujano R, Penco JM, Nicolaides KH. Longitudinal changes in maternal serum placental growth factor and soluble fms-like tyrosine kinase-1 in women at increased risk of pre-eclampsia. Ultrasound Obstet Gynecol. 2016;47(3):324–31. https://doi.org/10.1002/uog.15750.
74. Rios DR, Alpoim PN, Godoi LC, Perucci LO, de Sousa LP, Gomes KB et al. Increased levels of sENG and sVCAM-1 and decreased levels of VEGF in severe preeclampsia. Am J Hypertens. 2015.
75. March MI, Geahchan C, Wenger J, Raghuraman N, Berg A, Haddow H, et al. Circulating angiogenic factors and the risk of adverse outcomes among Haitian women with preeclampsia. PLoS One. 2015;10(5):e0126815. https://doi.org/10.1371/journal.pone.0126815.
76. Crovetto F, Figueras F, Triunfo S, Crispi F, Rodriguez-Sureda V, Peguero A, et al. Added value of angiogenic factors for the prediction of early and late preeclampsia in the first trimester of pregnancy. Fetal Diagn Ther. 2014;35(4):258–66. https://doi.org/10.1159/000358302.
77. Hund M, Allegranza D, Schoedl M, Dilba P, Verhagen-Kamerbeek W, Stepan H. Multicenter prospective clinical study to evaluate the prediction of short-term outcome in pregnant women with suspected preeclampsia (PROGNOSIS): study protocol. BMC Pregnancy Childbirth. 2014;14:324. https://doi.org/10.1186/1471-2393-14-324.
78. Herraiz I, Droge LA, Gomez-Montes E, Henrich W, Galindo A, Verlohren S. Characterization of the soluble fms-like tyrosine kinase-1 to placental growth factor ratio in pregnancies complicated by fetal growth restriction. Obstet Gynecol. 2014;124(2 Pt 1):265–73. https://doi.org/10.1097/AOG.0000000000000367.
79. Leanos-Miranda A, Campos-Galicia I, Isordia-Salas I, Rivera-Leanos R, Romero-Arauz JF, Ayala-Mendez JA, et al. Changes in circulating concentrations of soluble fms-like tyrosine kinase-1 and placental growth factor measured by automated electrochemiluminescence immunoassays methods are predictors of preeclampsia. J Hypertens. 2012;30(11):2173–81. https://doi.org/10.1097/HJH.0b013e328357c0c9.
80. Paez MC, Serrano NC, Diaz LA, Beltran MA, Ortiz R, Monterrosa A, et al. O2. Serum concentrations of angiogenic factors as predictors of severity of preeclampsia, in Colombian population. Pregnancy Hypertens. 2011;1(3–4):258. https://doi.org/10.1016/j.preghy.2011.08.034.
81. Kusanovic JP, Romero R, Chaiworapongsa T, Erez O, Mittal P, Vaisbuch E, et al. A prospective cohort study of the value of maternal plasma concentrations of angiogenic and antiangiogenic factors in early pregnancy and midtrimester in the identification of patients destined to develop preeclampsia. J Matern Fetal Neonatal Med. 2009;22(11):1021–38. https://doi.org/10.3109/14767050902994754.
82. Chedraui P, Lockwood CJ, Schatz F, Buchwalder LF, Schwager G, Guerrero C, et al. Increased plasma soluble fms-like tyrosine kinase 1 and endoglin levels in pregnancies complicated with preeclampsia. J Matern Fetal Neonatal Med. 2009;22(7):565–70. https://doi.org/10.1080/14767050902801769.

83. Giorgi VS, Witkin SS, Bannwart-Castro CF, Sartori MS, Romao-Veiga M, Borges VT, et al. Elevated circulatingadenosine deaminase activity in women with preeclampsia: association with pro-inflammatory cytokine production and uric acid levels. Pregnancy Hypertens. 2016;6(4):400–5.
84. Poveda NE, Garces MF, Ruiz-Linares CE, Varon D, Valderrama S, Sanchez E, et al. Serum adipsin levels throughout normal pregnancy and preeclampsia. Sci Rep. 2016;6:20073. https://doi.org/10.1038/srep20073.
85. Perucci LO, Vieira EL, Teixeira AL, Gomes KB, Dusse LM, Sousa LP. Decreased plasma concentrations of brain-derived neurotrophic factor in preeclampsia. Clin Chim Acta. 2017;464:142–7.
86. Teran E, Escudero C, Calle A. C-reactive protein during normal pregnancy and preeclampsia. Int J Gynaecol Obstet. 2005;89(3):299–300. https://doi.org/10.1016/j.ijgo.2005.02.002.
87. Lopez-Hernandez Y, Saldivar-Nava JA, Garza-Veloz I, Delgado-Enciso I, Martinez-de-Villarreal LE, Yahuaca-Mendoza P, et al. Nested case-control study reveals increased levels of urinary proteins from human kidney toxicity panels in women predicted to develop preeclampsia. Int Urol Nephrol. 2016;48(12):2051–9. https://doi.org/10.1007/s11255-016-1397-6.
88. Aban C, Leguizamon GF, Cella M, Damiano A, Franchi AM, Farina MG. Differential expression of endocannabinoid system in normal and preeclamptic placentas: effects on nitric oxide synthesis. Placenta. 2013;34(1):67–74. https://doi.org/10.1016/j.placenta.2012.10.009.
89. Parra-Cordero M, Sepulveda-Martinez A, Preisler J, Pasten J, Soto-Chacon E, Valdes E, et al. Role of the glucose tolerance test as a predictor of preeclampsia. Gynecol Obstet Investig. 2014;78(2):130–5. https://doi.org/10.1159/000358876.
90. Martinez-Fierro ML, Perez-Favila A, Garza-Veloz I, Espinoza-Juarez MA, Avila-Carrasco L, Delgado-Enciso I, et al. Matrix metalloproteinase multiplex screening identifies increased MMP-2 urine concentrations in women predicted to develop preeclampsia. Biomarkers. 2017:1–7. https://doi.org/10.1080/1354750X.2017.1279214.
91. Palei AC, Sandrim VC, Amaral LM, Machado JS, Cavalli RC, Duarte G, et al. Association between matrix metalloproteinase (MMP)-2 polymorphisms and MMP-2 levels in hypertensive disorders of pregnancy. Exp Mol Pathol. 2012;92(2):217–21. https://doi.org/10.1016/j.yexmp.2012.01.008.
92. Garces MF, Sanchez E, Cardona LF, Simanca EL, Gonzalez I, Leal LG, et al. Maternal serum meteorin levels and the risk of preeclampsia. PLoS One. 2015;10(6):e0131013. https://doi.org/10.1371/journal.pone.0131013.
93. Perez-Sepulveda A, Torres MJ, Valenzuela FJ, Larrain R, Figueroa-Diesel H, Galaz J, et al. Low 2-methoxyestradiol levels at the first trimester of pregnancy are associated with the development of pre-eclampsia. Prenat Diagn. 2012;32(11):1053–8. https://doi.org/10.1002/pd.3954.
94. Palacios de Franco Y, Velazquez K, Segovia N, Acosta C, Yanosky D, Franco Palacios YV, et al. Urinary podocalyxin as a marker of preeclampsia in a Hispanic population. Int J Physiol Pathophysiol Pharmacol. 2014;6(2):115–24.
95. Dietrich V, Szpilbarg N, Damiano AE. Reduced expression of Na(+)/H(+) exchanger isoform 3 (NHE-3) in preeclamptic placentas. Placenta. 2013;34(9):828–30. https://doi.org/10.1016/j.placenta.2013.06.005.
96. Chamy VM, Lepe J, Catalan A, Retamal D, Escobar JA, Madrid EM. Oxidative stress is closely related to clinical severity of pre-eclampsia. Biol Res. 2006;39(2):229–36.
97. Ayala-Ramirez P, Buitrago T, Poveda A, Rodriguez JL, Olaya CM, Garcia-Robles R. Increased tissue factor and thrombomodulin expression and histopathological changes in placentas of pregnancies with preeclampsia. J Neonatal Perinatal Med. 2016;9(1):31–9. https://doi.org/10.3233/NPM-16915034.
98. von Dadelszen P, Payne B, Li J, Ansermino JM, Broughton Pipkin F, Cote AM, et al. Prediction of adverse maternal outcomes in pre-eclampsia: development and validation of the fullPIERS model. Lancet. 2011;377(9761):219–27. https://doi.org/10.1016/S0140-6736(10)61351-7.
99. Almeida ST, Katz L, Coutinho I, Amorim MMR. Validation of fullPIERS model for prediction of adverse outcomes among women with severe pre-eclampsia. Int J Gynaecol Obstet. 2017; https://doi.org/10.1002/ijgo.12197.
100. Haukkamaa L, Moilanen L, Kattainen A, Luoto R, Kahonen M, Leinonen M, et al. Pre-eclampsia is a risk factor of carotid artery atherosclerosis. Cerebrovasc Dis. 2009;27(6):599–607. https://doi.org/10.1159/000216834.
101. Agatisa PK, Ness RB, Roberts JM, Costantino JP, Kuller LH, McLaughlin MK. Impairment of endothelial function in women with a history of preeclampsia: an indicator of cardiovascular risk. Am J Physiol Heart Circ Physiol. 2004;286(4):H1389–93. https://doi.org/10.1152/ajpheart.00298.2003.
102. Davis EF, Lazdam M, Lewandowski AJ, Worton SA, Kelly B, Kenworthy Y, et al. Cardiovascular risk factors in children and young adults born to preeclamptic pregnancies: a systematic review. Pediatrics. 2012;129(6):e1552–61. https://doi.org/10.1542/peds.2011-3093.
103. Evans CS, Gooch L, Flotta D, Lykins D, Powers RW, Landsittel D, et al. Cardiovascular system during the postpartum state in women with a history of preeclampsia. Hypertension. 2011; https://doi.org/10.1161/HYPERTENSIONAHA.111.173278.
104. Valdes G, Quezada F, Marchant E, von Schultzendorff A, Moran S, Padilla O, et al. Association of remote hypertension in pregnancy with coronary artery disease: a case-control study. Hypertension. 2009;53(4):733–8. https://doi.org/10.1161/HYPERTENSIONAHA.108.127068.
105. Germain AM, Romanik MC, Guerra I, Solari S, Reyes MS, Johnson RJ, et al. Endothelial dysfunction: a link among preeclampsia, recurrent pregnancy loss, and future cardiovascular events? Hypertension. 2007;49(1):90–5. https://doi.org/10.1161/01.HYP.0000251522.18094.d4.
106. Galvão ACAdA. Sindrome metabólica e fatores de risco associados: estudo comparativo entre mulheres que apresentaram pre-eclampsia e gravidez normal, acompanhadas 5 anos após o parto. Tese de Doutorado, Universidade Federal do Rio Grande do Norte. 2013.
107. Silva MdLCd, Araújo ACPFd. Doenças cardiovasculares em mulheres com histórico de pré-eclampsia e segmento no Sistema Único de Saúde. Tese de Doutorado: Universidade Federal do Rio Grande do Norte. 2013.
108. Ferreira RM, Bazan SGZ, Martin LC. Cardiovascular risk factors in women with preeclampsia history and their association with myocardial hypertrophy and intima-media thickening of the carotids. Tese de Doutorado, Faculdade de Medicina, Universidade Estadual de São Paulo, Botucatu. 2016.
109. Henriques AC, Carvalho FH, Feitosa HN, Macena RH, Mota RM, Alencar JC. Endothelial dysfunction after pregnancy-induced hypertension. Int J Gynaecol Obstet. 2014;124(3):230–4. https://doi.org/10.1016/j.ijgo.2013.08.016.
110. Torrado J, Farro I, Zocalo Y, Farro F, Sosa C, Scasso S, et al. Preeclampsia is associated with increased central aortic pressure, elastic arteries stiffness and wave reflections, and resting and recruitable endothelial dysfunction. Int J Hypertens. 2015;2015:720683. https://doi.org/10.1155/2015/720683.
111. Serrano-Diaz N, Paez-Leal M, Beltran-Avendano M, Colmenares-Mejia C, Guio-Mahecha E, Bautista-Nino P, et al. Preeclampsia y riesgo cardiovascular: estudio de seguimiento en la poblacion de

GenPE en Colombia. Revista Colombiana de Obstetricia y Ginecologia. 2012;63(3):241–51.

112. Goynumer G, Yucel N, Adali E, Tan T, Baskent E, Karadag C. Vascular risk in women with a history of severe preeclampsia. J Clin Ultrasound. 2013;41(3):145–50. https://doi.org/10.1002/jcu.21962.

113. Blaauw J, van Pampus MG, Van Doormaal JJ, Fokkema MR, Fidler V, Smit AJ, et al. Increased intima-media thickness after early-onset preeclampsia. Obstet Gynecol. 2006;107(6):1345–51.

114. Blaauw J, Souwer ET, Coffeng SM, Smit AJ, van Doormaal JJ, Faas MM, et al. Follow up of intima-media thickness after severe early-onset preeclampsia. Acta Obstet Gynecol Scand. 2014;93(12):1309–16. https://doi.org/10.1111/aogs.12499.

115. Sandvik MK, Leirgul E, Nygard O, Ueland PM, Berg A, Svarstad E, et al. Preeclampsia in healthy women and endothelial dysfunction 10 years later. Am J Obstet Gynecol. 2013;209(6):569 e1–e10. https://doi.org/10.1016/j.ajog.2013.07.024.

116. Franz MB, Burgmann M, Neubauer A, Zeisler H, Sanani R, Gottsauner-Wolf M, et al. Augmentation index and pulse wave velocity in normotensive and pre-eclamptic pregnancies. Acta Obstet Gynecol Scand. 2013;92(8):960–6. https://doi.org/10.1111/aogs.12145.

117. Karkkainen H, Saarelainen H, Laitinen T, Heiskanen N, Valtonen P, Vanninen E, et al. Ambulatory arterial stiffness index and nocturnal blood pressure dipping in pregnancies complicated by hypertension. Clin Physiol Funct Imaging. 2014;34(1):39–46. https://doi.org/10.1111/cpf.12063.

118. Ehrenthal DB, Goldstein ND, Wu P, Rogers S, Townsend RR, Edwards DG. Arterial stiffness and wave reflection 1 year after a pregnancy complicated by hypertension. J Clin Hypertens (Greenwich). 2014;16(10):695–9. https://doi.org/10.1111/jch.12398.

119. Grand'Maison S, Pilote L, Okano M, Landry T, Dayan N. Markers of vascular dysfunction after hypertensive disorders of pregnancy: a systematic review and meta-analysis. Hypertension. 2016;68(6):1447–58.

120. Harville EW, Juonala M, Viikari JS, Kahonen M, Raitakari OT. Vascular ultrasound measures before pregnancy and pregnancy complications: a prospective cohort study. Hypertens Pregnancy. 2016;36:1–6. https://doi.org/10.1080/10641955.2016.1237643.

121. Akhter T, Wikstrom AK, Larsson M, Larsson A, Wikstrom G, Naessen T. Association between angiogenic factors and signs of arterial aging in women with pre-eclampsia. Ultrasound Obstet Gynecol. 2016; https://doi.org/10.1002/uog.15981.

122. Marin R, Gorostidi M, Portal CG, Sanchez M, Sanchez E, Alvarez J. Long-term prognosis of hypertension in pregnancy. Hypertens Pregnancy. 2000;19(2):199–209.

123. Dantas EM, Pereira FV, Queiroz JW, Dantas DL, Monteiro GR, Duggal P, et al. Preeclampsia is associated with increased maternal body weight in a northeastern Brazilian population. BMC Pregnancy Childbirth. 2013;13:159. https://doi.org/10.1186/1471-2393-13-159.

124. Abalos E, Cuesta C, Carroli G, Qureshi Z, Widmer M, Vogel JP, et al. Pre-eclampsia, eclampsia and adverse maternal and perinatal outcomes: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. BJOG. 2014;121(Suppl 1):14–24. https://doi.org/10.1111/1471-0528.12629.

125. Wiegman MJ, Zeeman GG, Aukes AM, Bolte AC, Faas MM, Aarnoudse JG, et al. Regional distribution of cerebral white matter lesions years after preeclampsia and eclampsia. Obstet Gynecol. 2014;123(4):790–5. https://doi.org/10.1097/AOG.0000000000000162.

126. Aukes AM, de Groot JC, Aarnoudse JG, Zeeman GG. Brain lesions several years after eclampsia. Am J Obstet Gynecol. 2009;200(5):504 e1–5. https://doi.org/10.1016/j.ajog.2008.12.033.

127. Aukes AM, De Groot JC, Wiegman MJ, Aarnoudse JG, Sanwikarja GS, Zeeman GG. Long-term cerebral imaging after pre-eclampsia. BJOG. 2012;119(9):1117–22. https://doi.org/10.1111/j.1471-0528.2012.03406.x.

128. Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. Eur J Epidemiol. 2013;28(1):1–19. https://doi.org/10.1007/s10654-013-9762-6.

129. Siepmann T, Boardman H, Bilderbeck A, Griffanti L, Kenworthy Y, Zwager C, et al. Long-term cerebral white and gray matter changes after preeclampsia. Neurology. 2017;88(13):1256–64. https://doi.org/10.1212/WNL.0000000000003765.

130. Logue OC, George EM, Bidwell GL 3rd. Preeclampsia and the brain: neural control of cardiovascular changes during pregnancy and neurological outcomes of preeclampsia. Clin Sci (Lond). 2016;130(16):1417–34. https://doi.org/10.1042/CS20160108.

131. Alves Borges JH, Goes DA, de Araujo LB, Dos Santos MC, Debs Diniz AL. Prospective study of the hemodynamic behavior of ophthalmic arteries in postpartum preeclamptic women: a Doppler evaluation. Hypertens Pregnancy. 2016;35(1):100–11. https://doi.org/10.3109/10641955.2015.1116553.

132. Wiegman MJ, de Groot JC, Jansonius NM, Aarnoudse JG, Groen H, Faas MM, et al. Long-term visual functioning after eclampsia. Obstet Gynecol. 2012;119(5):959–66. https://doi.org/10.1097/AOG.0b013e31824da5a8.

133. Vikse BE, Irgens LM, Bostad L, Iversen BM. Adverse perinatal outcome and later kidney biopsy in the mother. J Am Soc Nephrol. 2006;17(3):837–45.

134. Henao DE, Arias LF, Mathieson PW, Ni L, Welsh GI, Bueno JC, et al. Preeclamptic sera directly induce slit-diaphragm protein redistribution and alter podocyte barrier-forming capacity. Nephron Exp Nephrol. 2008;110(3):e73–81. https://doi.org/10.1159/000166993.

135. Penning ME, Bloemenkamp KW, van der Zon T, Zandbergen M, Schutte JM, Bruijn JA, et al. Association of preeclampsia with podocyte turnover. Clin J Am Soc Nephrol. 2014;9(8):1377–85. https://doi.org/10.2215/CJN.12811213.

136. White WM, Garrett AT, Craici IM, Wagner SJ, Fitz-Gibbon PD, Butters KA, et al. Persistent urinary podocyte loss following pre-eclampsia may reflect subclinical renal injury. PLoS One. 2014;9(3):e92693. https://doi.org/10.1371/journal.pone.0092693.

137. Shahbazian N, Shahbazian H, Ehsanpour A, Aref A, Gharibzadeh S. Hypertension and microalbuminuria 5 years after pregnancies complicated by pre-eclampsia. Iran J Kidney Dis. 2011;5(5):324–7.

138. Gaugler-Senden IP, Berends AL, de Groot CJ, Steegers EA. Severe, very early onset preeclampsia: subsequent pregnancies and future parental cardiovascular health. Eur J Obstet Gynecol Reprod Biol. 2008;140(2):171–7. https://doi.org/10.1016/j.ejogrb.2008.03.004.

139. Shammas AG, Maayah JF. Hypertension and its relation to renal function 10 years after pregnancy complicated by pre-eclampsia and pregnancy induced hypertension. Saudi Med J. 2000;21(2):190–2.

140. Bar J, Kaplan B, Wittenberg C, Erman A, Boner G, Ben-Rafael Z, et al. Microalbuminuria after pregnancy complicated by pre-eclampsia. Nephrol Dial Transplant. 1999;14(5):1129–32.

141. Nisell H, Lintu H, Lunell NO, Mollerstrom G, Pettersson E. Blood pressure and renal function seven years after pregnancy complicated by hypertension. Br J Obstet Gynaecol. 1995;102(11):876–81.

142. Sandvik MK, Hallan S, Svarstad E, Vikse BE. Preeclampsia and prevalence of microalbuminuria 10 years later. Clin J Am Soc

Nephrol. 2013;8(7):1126–34. https://doi.org/10.2215/CJN.10641012.

143. Vikse BE, Hallan S, Bostad L, Leivestad T, Iversen BM. Previous preeclampsia and risk for progression of biopsy-verified kidney disease to end-stage renal disease. Nephrol Dial Transplant. 2010;25(10):3289–96. https://doi.org/10.1093/ndt/gfq169.

144. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ. 2007;335(7627):974. https://doi.org/10.1136/bmj.39335.385301.BE.

145. Lawlor DA, Macdonald-Wallis C, Fraser A, Nelson SM, Hingorani A, Davey Smith G, et al. Cardiovascular biomarkers and vascular function during childhood in the offspring of mothers with hypertensive disorders of pregnancy: findings from the Avon Longitudinal Study of Parents and Children. Eur Heart J. 2012;33(3):335–45. https://doi.org/10.1093/eurheartj/ehr300.

146. Kajantie E, Eriksson JG, Osmond C, Thornburg K, Barker DJ. Pre-eclampsia is associated with increased risk of stroke in the adult offspring: the Helsinki birth cohort study. Stroke. 2009;40(4):1176–80.

147. Wu CS, Nohr EA, Bech BH, Vestergaard M, Catov JM, Olsen J. Health of children born to mothers who had preeclampsia: a population-based cohort study. Am J Obstet Gynecol. 2009;201(3):269 e1–e10. https://doi.org/10.1016/j.ajog.2009.06.060.

148. Wu CS, Nohr EA, Bech BH, Vestergaard M, Catov JM, Olsen J. Diseases in children born to mothers with preeclampsia: a population-based sibling cohort study. Am J Obstet Gynecol. 2011;204(2):157 e1–5. https://doi.org/10.1016/j.ajog.2010.08.046.

149. Bellizzi S, Ali MM, Abalos E, Betran AP, Kapila J, Pileggi-Castro C, et al. Are hypertensive disorders in pregnancy associated with congenital malformations in offspring? Evidence from the WHO multicountry cross sectional survey on maternal and newborn health. BMC Pregnancy Childbirth. 2016;16(1):198. https://doi.org/10.1186/s12884-016-0987-8.

150. Alsnes IV, Vatten LJ, Fraser A, Bjorngaard JH, Rich-Edwards J, Romundstad PR, et al. Hypertension in pregnancy and offspring cardiovascular risk in young adulthood: prospective and sibling studies in the HUNT study (Nord-Trondelag Health Study) in Norway. Hypertension. 2017;69(4):591–8. https://doi.org/10.1161/HYPERTENSIONAHA.116.08414.

151. Yu GZ, Leeson P. Hypertension: hypertension in pregnancy: a risk factor for the whole family? Nat Rev Nephrol. 2017;13(6):326–7. https://doi.org/10.1038/nrneph.2017.54.

152. Timpka S, Macdonald-Wallis C, Hughes AD, Chaturvedi N, Franks PW, Lawlor DA et al. Hypertensive disorders of pregnancy and offspring cardiac structure and function in adolescence. J Am Heart Assoc. 2016;5(11). https://doi.org/10.1161/JAHA.116.003906.

153. Yesil GD, Gishti O, Felix JF, Reiss I, Ikram MK, Steegers EA, et al. Influence of maternal gestational hypertensive disorders on microvasculature in school-age children: the generation R study. Am J Epidemiol. 2016;184(9):605–15. https://doi.org/10.1093/aje/kww059.

154. Yu GZ, Aye CY, Lewandowski AJ, Davis EF, Khoo CP, Newton L, et al. Association of maternal antiangiogenic profile at birth with early postnatal loss of microvascular density in offspring of hypertensive pregnancies. Hypertension. 2016;68(3):749–59. https://doi.org/10.1161/HYPERTENSIONAHA.116.07586.

155. Ratsep MT, Paolozza A, Hickman AF, Maser B, Kay VR, Mohammad S, et al. Brain structural and vascular anatomy is altered in offspring of pre-eclamptic pregnancies: a pilot study. AJNR Am J Neuroradiol. 2016;37(5):939–45. https://doi.org/10.3174/ajnr.A4640.

156. Dang F, Croy BA, Stroman PW, Figueiro-Filho EA. Impacts of preeclampsia on the brain of the offspring. Rev Bras Ginecol Obstet. 2016;38(8):416–22. https://doi.org/10.1055/s-0036-1584515.

157. Ratsep MT, Hickman AF, Croy BA. The Elsevier trophoblast research award lecture: impacts of placental growth factor and pre-eclampsia on brain development, behaviour, and cognition. Placenta. 2016;48(Suppl 1):S40–S6.

158. Tuovinen S, Raikkonen K, Kajantie E, Pesonen AK, Heinonen K, Osmond C, et al. Depressive symptoms in adulthood and intrauterine exposure to pre-eclampsia: the Helsinki Birth Cohort Study. BJOG. 2010;117(10):1236–42. https://doi.org/10.1111/j.1471-0528.2010.02634.x.

159. Szymonowicz W, Yu VY. Severe pre-eclampsia and infants of very low birth weight. Arch Dis Child. 1987;62(7):712–6.

160. Cheng SW, Chou HC, Tsou KI, Fang LJ, Tsao PN. Delivery before 32 weeks of gestation for maternal pre-eclampsia: neonatal outcome and 2-year developmental outcome. Early Hum Dev. 2004;76(1):39–46.

161. Griffith MI, Mann JR, McDermott S. The risk of intellectual disability in children born to mothers with preeclampsia or eclampsia with partial mediation by low birth weight. Hypertens Pregnancy. 2011;30(1):108–15. https://doi.org/10.3109/10641955.2010.507837.

162. Johnson S, Evans TA, Draper ES, Field DJ, Manktelow BN, Marlow N, et al. Neurodevelopmental outcomes following late and moderate prematurity: a population-based cohort study. Arch Dis Child Fetal Neonatal Ed. 2015;100(4):F301–8. https://doi.org/10.1136/archdischild-2014-307684.

163. Ratsep MT, Hickman AF, Maser B, Pudwell J, Smith GN, Brien D, et al. Impact of preeclampsia on cognitive function in the offspring. Behav Brain Res. 2016;302:175–81. https://doi.org/10.1016/j.bbr.2016.01.030.

164. Whitehouse AJ, Robinson M, Newnham JP, Pennell CE. Do hypertensive diseases of pregnancy disrupt neurocognitive development in offspring? Paediatr Perinat Epidemiol. 2012;26(2):101–8. https://doi.org/10.1111/j.1365-3016.2011.01257.x.

165. Robinson M, Mattes E, Oddy WH, de Klerk NH, Li J, McLean NJ, et al. Hypertensive diseases of pregnancy and the development of behavioral problems in childhood and adolescence: the Western Australian Pregnancy Cohort Study. J Pediatr. 2009;154(2):218–24. https://doi.org/10.1016/j.jpeds.2008.07.061.

166. Alsnes IV, Janszky I, Asvold BO, Okland I, Forman MR, Vatten LJ. Maternal preeclampsia and androgens in the offspring around puberty: a follow-up study. PLoS One. 2016;11(12):e0167714. https://doi.org/10.1371/journal.pone.0167714.

167. Boeldt DS, Bird IM. Vascular adaptation in pregnancy and endothelial dysfunction in preeclampsia. J Endocrinol. 2017;232(1):R27–44. https://doi.org/10.1530/JOE-16-0340.

168. Sanchez-Aranguren LC, Prada CE, Riano-Medina CE, Lopez M. Endothelial dysfunction and preeclampsia: role of oxidative stress. Front Physiol. 2014;5:372. https://doi.org/10.3389/fphys.2014.00372.

169. Weissgerber TL, Turner ST, Mosley TH Jr, Kardia SL, Hanis CL, Milic NM, et al. Hypertension in pregnancy and future cardiovascular event risk in siblings. J Am Soc Nephrol. 2016;27(3):894–902. https://doi.org/10.1681/ASN.2015010086.

170. Teran E, Chedraui P, Vivero S, Villena F, Duchicela F, Nacevilla L. Plasma and placental nitric oxide levels in women with and without pre-eclampsia living at different altitudes. Int J Gynaecol Obstet. 2009;104(2):140–2. https://doi.org/10.1016/j.ijgo.2008.09.010.

171. Teran E, Escudero C, Moya W. Abnormal release of nitric oxide from nitrosoprotein in preeclampsia. Int J Gynaecol Obstet. 2006;92(3):260–1. https://doi.org/10.1016/j.ijgo.2005.12.015.

172. Acauan Filho BJ, Pinheiro da Costa BE, Ogando PB, Vieira MC, Antonello IC, Poli-de-Figueiredo CE. Serum nitrate and NOx levels in preeclampsia are higher than in normal pregnancy. Hypertens Pregnancy. 2016;35(2):226–33. https://doi.org/10.3109/10641955.2016.1139718.

173. Serrano NC, Casas JP, Diaz LA, Paez C, Mesa CM, Cifuentes R, et al. Endothelial NO synthase genotype and risk of preeclampsia: a multicenter case-control study. Hypertension. 2004;44(5):702–7. https://doi.org/10.1161/01.HYP.0000143483.66701.ec.

174. Corthorn J, Germain AA, Chacon C, Rey S, Soto GX, Figueroa CD, et al. Expression of kallikrein, bradykinin b2 receptor, and endothelial nitric oxide synthase in placenta in normal gestation, preeclampsia, and placenta accreta. Endocrine. 2006;29(3):491–9. https://doi.org/10.1385/ENDO:29:3:491.

175. Smith-Jackson K, Hentschke MR, Poli-de-Figueiredo CE, Pinheiro da Costa BE, Kurlak LO, Broughton Pipkin F, et al. Placental expression of eNOS, iNOS and the major protein components of caveolae in women with pre-eclampsia. Placenta. 2015;36(5):607–10. https://doi.org/10.1016/j.placenta.2015.02.001.

176. Casanello P, Escudero C, Sobrevia L. Equilibrative nucleoside (ENTs) and cationic amino acid (CATs) transporters: implications in foetal endothelial dysfunction in human pregnancy diseases. Curr Vasc Pharmacol. 2007;5(1):69–84.

177. Sandrim VC, Palei AC, Metzger IF, Gomes VA, Cavalli RC, Tanus-Santos JE. Nitric oxide formation is inversely related to serum levels of antiangiogenic factors soluble fms-like tyrosine kinase-1 and soluble endogline in preeclampsia. Hypertension. 2008;52(2):402–7. https://doi.org/10.1161/HYPERTENSIONAHA.108.115006.

178. Gishti O, Jaddoe VW, Felix JF, Klaver CC, Hofman A, Wong TY, et al. Retinal microvasculature and cardiovascular health in childhood. Pediatrics. 2015;135(4):678–85. https://doi.org/10.1542/peds.2014-3341.

179. de Oliveira CA, de Sa RA, Velarde LG, da Silva FC, doVale FA, Netto HC. Changes in ophthalmic artery Doppler indices in hypertensive disorders during pregnancy. J Ultrasound Med. 2013;32(4):609–16.

180. Oliveira CA, Sa RA, Velarde LG, Silva FC, Netto HC. PP082. Ophthalmic artery Doppler for identification of severe preeclampsia in pregnancies complicated by hypertension. Pregnancy Hypertens. 2012;2(3):284–5. https://doi.org/10.1016/j.preghy.2012.04.193.

181. Wenceslau CF, McCarthy CG, Szasz T, Spitler K, Goulopoulou S, Webb RC. Mitochondrial damage-associated molecular patterns and vascular function. Eur Heart J. 2014;35(18):1172–7. https://doi.org/10.1093/eurheartj/ehu047.

182. Goulopoulou S, Matsumoto T, Bomfim GF, Webb RC. Toll-like receptor 9 activation: a novel mechanism linking placenta-derived mitochondrial DNA and vascular dysfunction in pre-eclampsia. Clin Sci (Lond). 2012;123(7):429–35. https://doi.org/10.1042/CS20120130.

183. McCarthy CM, Kenny LC. Mitochondrial [dys]function; culprit in pre-eclampsia? Clin Sci (Lond). 2016;130(14):1179–84. https://doi.org/10.1042/CS20160103.

184. Huppertz B, Kingdom JC. Apoptosis in the trophoblast—role of apoptosis in placental morphogenesis. J Soc Gynecol Investig. 2004;11(6):353–62. https://doi.org/10.1016/j.jsgi.2004.06.002.

185. McCarthy CM, Kenny LC. Immunostimulatory role of mitochondrial DAMPs: alarming for pre-eclampsia? Am J Reprod Immunol. 2016;76(5):341–7. https://doi.org/10.1111/aji.12526.

186. Verdegem D, Moens S, Stapor P, Carmeliet P. Endothelial cell metabolism: parallels and divergences with cancer cell metabolism. Cancer Metab. 2014;2:19. https://doi.org/10.1186/2049-3002-2-19.

187. Afzal-Ahmed I, Mann GE, Shennan AH, Poston L, Naftalin RJ. Preeclampsia inactivates glucose-6-phosphate dehydrogenase and impairs the redox status of erythrocytes and fetal endothelial cells. Free Radic Biol Med. 2007;42(12):1781–90. https://doi.org/10.1016/j.freeradbiomed.2007.02.032.

188. Wadhwani N, Patil V, Pisal H, Joshi A, Mehendale S, Gupte S, et al. Altered maternal proportions of long chain polyunsaturated fatty acids and their transport leads to disturbed fetal stores in preeclampsia. Prostaglandins Leukot Essent Fatty Acids. 2014;91(1–2):21–30. https://doi.org/10.1016/j.plefa.2014.05.006.

189. Diaz-Olguin L, Coral-Vazquez RM, Canto-Cetina T, Canizales-Quinteros S, Ramirez Regalado B, Fernandez G, et al. Endothelial nitric oxide synthase haplotypes are associated with preeclampsia in Maya mestizo women. Dis Markers. 2011;31(2):83–9. https://doi.org/10.3233/DMA-2011-0804.

190. Sandrim VC, Palei AC, Cavalli RC, Araujo FM, Ramos ES, Duarte G, et al. eNOS haplotypes associated with gestational hypertension or preeclampsia. Pharmacogenomics. 2008;9(10):1467–73. https://doi.org/10.2217/14622416.9.10.1467.

191. Leonardo DP, Albuquerque DM, Lanaro C, Baptista LC, Cecatti JG, Surita FG, et al. Association of nitric oxide synthase and matrix metalloprotease single nucleotide polymorphisms with preeclampsia and its complications. PLoS One. 2015;10(8):e0136693. https://doi.org/10.1371/journal.pone.0136693.

192. Julian CG, Pedersen BS, Salmon CS, Yang IV, Gonzales M, Vargas E, et al. Unique DNA methylation patterns in offspring of hypertensive pregnancy. Clin Transl Sci. 2015;8(6):740–5. https://doi.org/10.1111/cts.12346.

193. Van Noorden R. The impact gap: South America by the numbers. Nature. 2014;510(7504):202–3. https://doi.org/10.1038/510202a.

194. Fisberg M, Kovalskys I, Gomez G, Rigotti A, Cortes LY, Herrera-Cuenca M, et al. Latin American Study of Nutrition and Health (ELANS): rationale and study design. BMC Public Health. 2016;16:93. https://doi.org/10.1186/s12889-016-2765-y.

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