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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

This article is part of the Topical Collection on *Preeclampsia*

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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/uL) 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 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 (min)
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

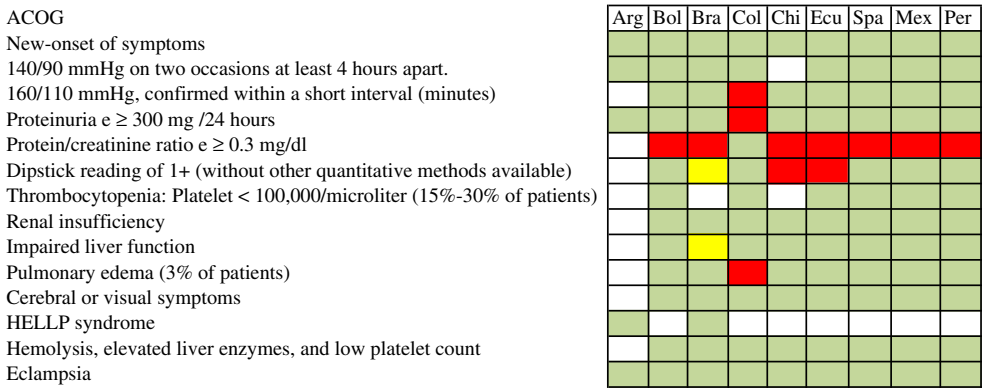


**Fig. 1** Percentage of accomplishment of the ACOG diagnosis criteria for preeclampsia in Latin-American countries. For this figure, official guidelines for diagnosis of preeclampsia from Latin-American countries including Argentina (Arg), Bolivia (Bol), Brazil (Bra), Colombia (Col), Chile (Chi), Ecuador (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

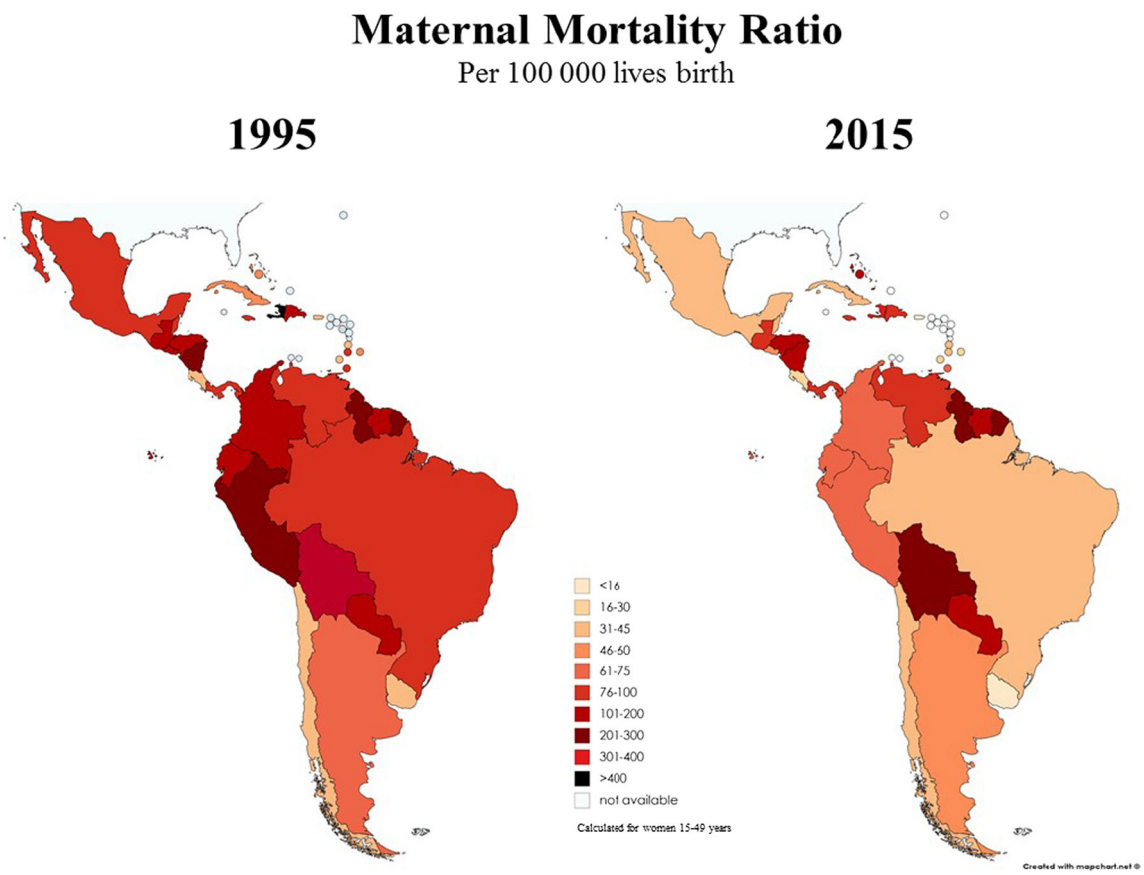


**Fig. 2** Maternal mortality ratio calculated per 100,000 live births from 1995 to 2015. Compiled data from WHO, UNICEF, UNFPA, World Bank group, and United Nations Population Division, available at WWW.who.int/maternal_health. Boxes in colors represent rate per 100.000 habitants in respective countries

hypertensive disorders observed during pregnancy, particularly preeclampsia, complicate 10 million pregnancies, resulting 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

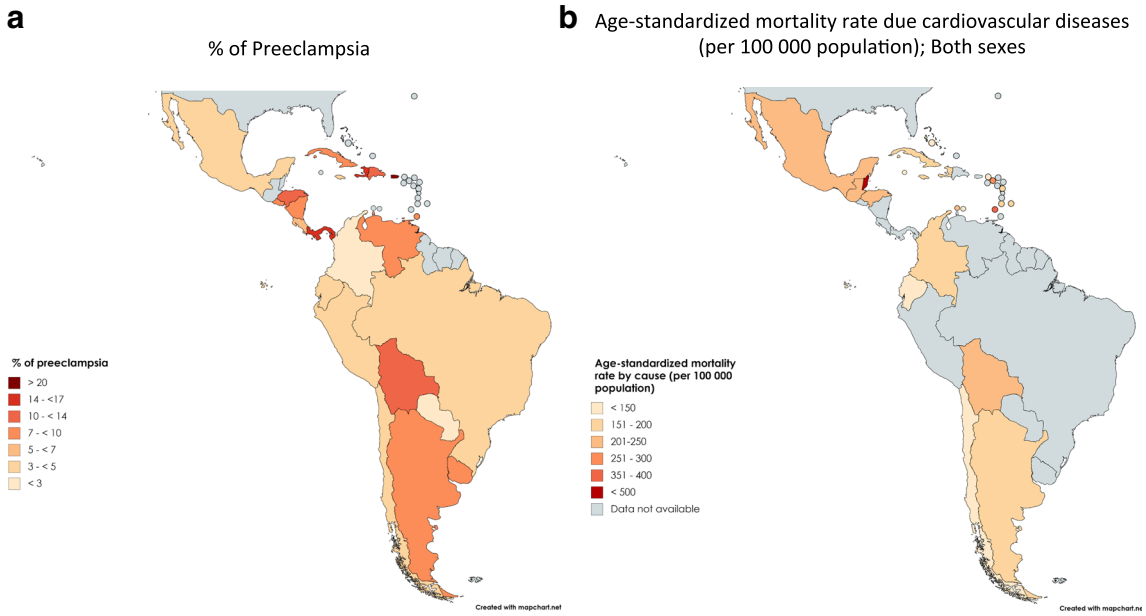


**Fig. 3** Rate of preeclampsia and cardiovascular disease in Latin-American countries. Information about rate of preeclampsia in Latin-American countries was exhaustively search from different sources (references are available under request). Also, rate of cardiovascular disease was obtained from the World Health Organization database (2012). **a** Rate of preeclampsia. Panel represent rate (%) of preeclampsia considering all pregnancies in each country. **b** Cardiovascular mortality due to cardiovascular disease. Panel represent Age-standardize mortality rate in both male and female per 100 000 habitants.

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 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

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

| 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 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

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.

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

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

| 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 | MMP | 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

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.

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

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

| Country | Study | Sample size | Finding in preeclampsia | Reference |
|---|---|---|---|---|
| Uruguay | Case-control | 7 PE, 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

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 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 [153]. 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

**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 | Increased risk of a variety of diseases, such as endocrine, nutritional, and metabolic diseases; as well as disease of the blood and blood-forming organs | [147] |
| 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] |

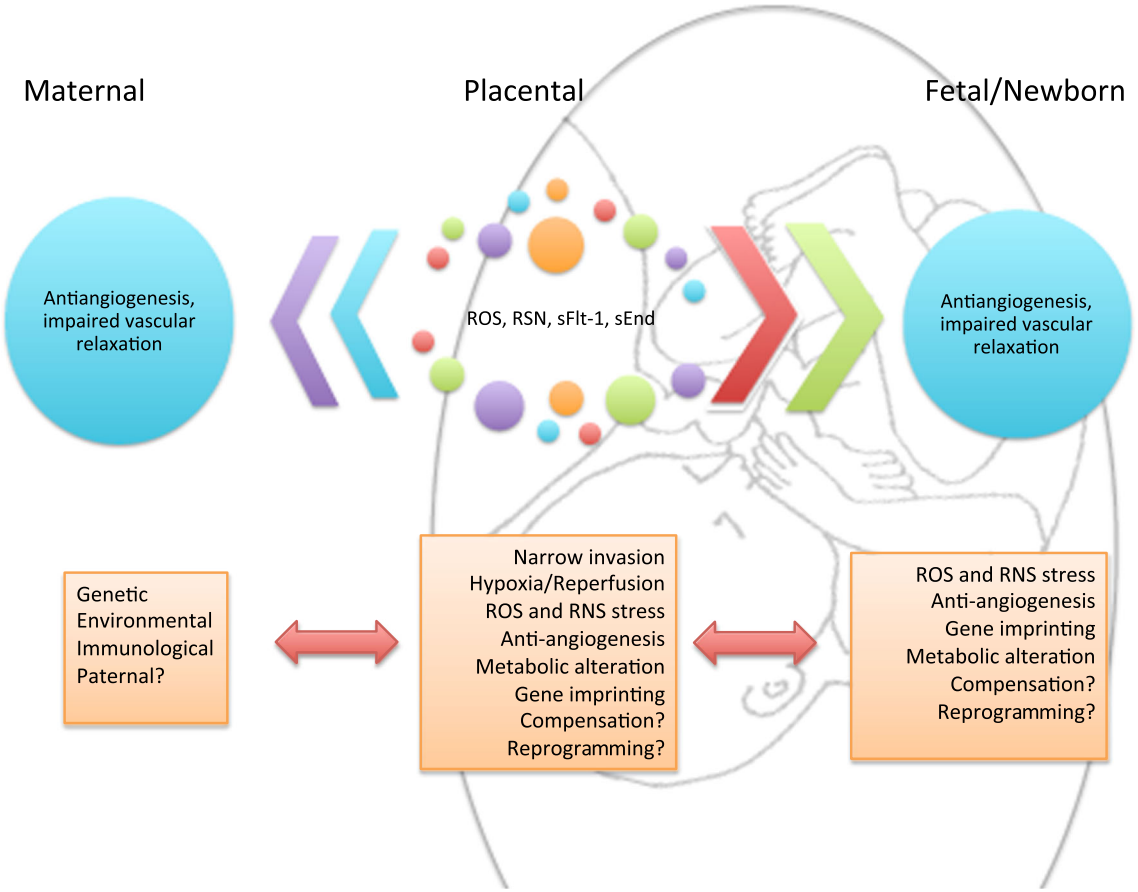


**Fig. 4** Endothelial dysfunction in maternal, placental, and fetal circulation in preeclampsia. Interaction between maternal, placental, and fetal/newborn compartments. Ischemic placenta can release several signaling molecules into both maternal and fetal compartment, which have been associated with 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

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.

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

In order to be proactive, we highlight some potential mechanisms that may account for studying endothelial dysfunction in preeclampsia. Thus, 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 McCarthy et al. [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 Latin American 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 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 discovered and tested 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 efficacious 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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