Vascular dysfunction in mother and offspring during preeclampsia: How Iberoamerican countries can contribute to the current discussion

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Running title: Inputs from Iberoamerican countries about endothelial dysfunction in preeclampsia

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Abstract

Pregnancy is a physiological stressful condition that generates a series of functional adaptations in the cardiovascular system. The impact of pregnancy on this system persist since conception to birth; and even, recent evidence suggests that vascular changes associated with pregnancy complications, such as preeclampsia, could affect the functionality of the maternal and offspring vascular system, after delivery and in their adult life, respectively. Since the vascular system is contributes to the systemic homeostasis, defective development or function of blood vessels might predispose both mother and descent to future risks for chronic diseases. These alterations, in future life, range from fertility problems to alterations in the central nervous system or immune system, among others. Of importance, in Iberoamerican countries, rates of morbimortality due to pregnancy complications including preeclampsia, as well as cardiovascular diseases, exhibited higher incidence than in developed countries. However, there is a lack both in number and in the impact of research conducted in Iberoamerica comprising these fields. Furthermore, smaller impact 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 coming from research groups based in Iberoamerican countries will be highlighted, not only as an auto reference study, but more importantly, aiming to encourage international collaboration for generating regional data, looking for particularities about this topic.

Keywords: Preeclampsia, Iberoamerican countries, vascular dysfunction, cardiovascular risk, fetal programming.

Introduction

Preeclampsia is a major cause of maternal and infant morbidity and mortality worldwide [1]. Stillbirth is more common in preeclamptic pregnancies while one third of infants of preeclamptic women are growth restricted [2, 3] and 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 mother and her children [4-12].

In this regard, endothelial dysfunction defined as a systemic pathological state characterized by an imbalance between vasodilator and vasoconstrictor molecules, produced by or acting on the endothelium, has been linked to development of preeclampsia and cardiovascular diseases [13, 14]. Thus, endothelial dysfunction has been considered a key component of preeclampsia pathophysiology since 80s [15, 16]. Since those days, several publications have described endothelial dysfunction in 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 this vascular dysfunction observed in these three compartments are the same is a question that remains unclear.

In Iberoamerican countries where preeclampsia constitute one of the leading causes of maternal and fetal mortality [23], information about this disease has been mainly related with what have been studied in developed countries. This means that information available about particularities related with this disease and its consequences in mother and their children, or even, in the future cardiovascular risk, is missing. In this article information about preeclampsia and endothelial dysfunction coming from research groups based in Iberoamerican countries will be revised, aiming to encourage generation of international and regional collaborations, focusing in elucidates regional particularities regarding vascular dysfunction both in mother and offspring, during preeclampsia.

Preeclampsia: General overview

Diagnosis 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]. In particular, the criteria include the presence of gestational hypertension: systolic blood pressure (SBP) >140/ diastolic blood pressure (DBP) > 90 mmHg; proteinuria: ≥ 0.3 g protein in 24 hours. Or in the absence of the last, the presence of headache, blurred vision, epigastric pain, thrombocytopenia (<100,000) 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 severe preeclampsia or eclampsia

(which includes seizures) [3, 23]. Recently, the Task Force on Hypertension in Pregnancy [28] eliminates the mild or severe preeclampsia denominations, instead, the group adopt the terms: preeclampsia without severity data or preeclampsia with severity data.

Iberoamerican countries adopted those criteria to generate specific guidelines. In Mexico, Peralta-Pedrero et al [29], besides the blood pressures values and urine protein levels, evaluated the usefulness of headache, phosphenes, acuphenes, tinnitus, vomiting, epigastric pain, right hypochondrium pain, ecchymosis, hematomas, and hyperreflexia, for establishing diagnosis and severity in preeclamptic patients. In their study, 84% of non preeclamptic patients presented less than three criterion; meanwhile, 50% of preeclamptic patients had more than three criterion [30].

In Ecuador, it was developed local guidelines (Guidelines for clinical practice in pregnancy hypertensive diseases), based on the criteria of the World Health Organization [31], which refers that pregnancy hypertension must be considered as a diastolic blood pressure values > 90 mm Hg. Hence, pressure values > 160/110 mmHg is a criterion used for severity. Dipstick ≥2+ strongly suggests proteinuria, which must be confirmed quantitatively with a protein urinary excretion of 0.3 g in 24 hours. Severity is demonstrated with urinary excretion of > 5g/24 h [32]

The diagnostic criteria established in the "*Guía Perinatal 2015*" (Perinatal Guide 2015) from the Ministry of Health in Chile, are based on the criteria of the American Colleague of Gynecologist, summarized by Sibai in 2003 [33]. In addition to those criteria, the guide also considers values of blood pressure <160/<110 mmHg and ≥160/≥110 mmHg as criteria for mild and severe preeclampsia respectively; diuresis < 500 mL in 24 hours for severe preeclampsia, central nervous system symptoms, thrombocytopenia, hemolysis and rise in hepatic enzymes are diagnostic criteria for severe preeclampsia [34].

In Argentina, the guidelines for diagnostic and treatment of pregnancy hypertensive diseases are based on different international and local guidelines. With these guidelines, criteria for mild and severe preeclampsia are the same as previously mentioned for Chile. But, in Argentina, others symptoms considered to classify severe preeclampsia are blurred vision, intrauterine growth restriction, oligohydramnios, placental detachment, cyanosis and acute pulmonary edema [35].

In Colombia, the diagnostic criteria are based to recommendation of the International Society for the Study of Hypertension in Pregnancy (ISSHP)[36]. The diagnostic of severe preeclampsia is established by blood pressure >160/110 mmHg or severe headache, blurred vision or phosphenes, severe hypochondrium pain, papilledema, clonus (≥ 3+), low platelet count (<150.000/mm^3), rise in hepatic enzymes [37].

Therefore, most of the Iberoamerican countries currently adopt diagnosis criteria for preeclampsia as stated by the American Colleague of Gynecologist. However, some particularities regarding diagnosis criteria for severity of the disease were found among Iberoamerican countries. For instance, in 2007, the technical guidelines for the diagnosis and management of preeclampsia in Mexico, define mild preeclampsia on the presence of blood

pressure values > 140/90 mm Hg and proteinuria of 0.3 g in 24 hours. Severe preeclampsia is diagnosed in the presence of blood pressure values >160/110 mm Hg, protein excretion in urine of more than 2 g in 24 hours, serum creatinine > 1.2 mg/dl, plaquetopenia ≤ 150 000 cel/mm3, lactate dehydrogenase (LDH) ≥ 600 UI, increased concentrations of hepatic enzymes, headache, visual and auditive disturbances, epigastric pain, growth restriction syndrome, oligohydramnios, oliguria ≤500 ml in 24 hours, pulmonary edema and right upper quadrant [Ministerio de Salud 30]

Epidemiology of preeclampsia: focus in Iberoamerica

Depending on the quality of the diagnosis criteria applied, the worldwide incidence of preeclampsia ranges from 3 and 10% of all pregnancies [23, 26, 38]. Each year, it is estimated that hypertension disorders observed during pregnancy, particularly preeclampsia, complicates 10 million pregnancies, resulting in 76,000 maternal and 500,000 fetal/newborn death worldwide [39]. Nearly all of these maternal deaths (>99%) occur in low-and middle-income countries [23]. In a study of hospitals managed by Health Care America Corporation, preeclampsia was the second leading cause of pregnancy-related intensive care unit admissions after obstetric hemorrhage [40].

Also, the incidence of preeclampsia is highly dependent on the availability and quality of obstetric care during gestation. Thus, while in developed countries range from 2-5% [2, 41], in developing countries, severe forms of preeclampsia and eclampsia are more common, ranging from as low as 4% of all deliveries, to as high as 18% in some parts of Africa [2]. Therefore, in those developing countries, a woman is seven times as likely to develop severe preeclampsia than a woman in a developed country.

Regarding mortality, the rates are also dependent on the country. A systematic review by the World Health Organization denotes that hypertensive disorders account for 16% of all maternal deaths in developed countries, while in developing countries 10-25% of the women will die as a consequence of a hypertensive disorder during pregnancy. Thus, preeclampsia accounts for 9% of maternal deaths in Africa and Asia, and as high as 26% in the Caribbean and Iberoamerican countries [42]. Thus, preeclampsia is the first cause of maternal death in Iberoamerica [Preeclampsia 43].

Particularly, a meta-analysis conducted by Abalos et al., found an incidence of preeclampsia and eclampsia of 3% and 0.7% respectively, in Americas. The authors provide crude incidence numbers for preeclampsia in four Iberoamerican countries: Argentina (10.0%), Brazil (1.5%), Chile (3.4%) and Mexico (5.5%). In the case of eclampsia, the numbers are: Argentina (0.4 %), Brazil (0.6 %), Chile (0.1 %) and Mexico (0.6) [44]. In 2014, a total of 872 maternal deaths were reported in Mexico where 20.5% of these deaths corresponded to hypertensive pregnancy diseases [30]. In this regard, Khan et al., reported that 25.7% of maternal deaths were attributable to

hypertensive disorders in Iberoamerica and the Caribbean [42]. Reaching a total of 3800 maternal death in 2011 in those countries [45]. Iberoamerican and Caribbean immigrants represent an increasing concern to developed countries, since they account for the highest rates of maternal mortality related to preeclampsia. This is more evident in Spain, where disparities in maternal attention between Spaniards and immigrants are accused [46]. Figure 1 include rate of preeclampsia and cardiovascular disease in Iberoamerica.

Studies have reported a 7-20% chance of preeclampsia recurrence in a subsequent pregnancy [47-49]. This risk is further increased if the woman had had two prior preeclamptic pregnancies, and is also influenced by gestational age of onset [50]. The recurrence of preeclampsia is also dependent on the diagnostic criteria. Thus, in a study performed in Iceland, the estimated recurrence of preeclampsia or superimposed preeclampsia in a second pregnancy was 13% [51]. In Iberoamerica, a study conducted in the northeast of Brazil demonstrated that most of the preeclamptic women tend to have controlled blood pressures after the third day of puerperium and are likely to be discharged from hospital still using anti-hypertensive drugs [52]. However, almost half of these patients were hospitalized during, at least, seven days and hypertensive emergencies occurred in 53.9% of them.

Also, preeclampsia is associated with adverse fetal outcomes. Thus, it has been estimated that 12 to 25% of fetal growth restriction and small for gestational age babies are associated to preeclampsia [26, 40]. Same study reports that the associated complications of prematurity due to preeclampsia are neonatal deaths and serious long-term neonatal morbidity [26, 40]. In Iberoamerica, studies carried out in Buenos Aires, Argentina analyzed the first year of life of babies born from 204 pregnancies with gestational hypertension and babies born from 147 normotensive pregnancies. Intrauterine growth restriction and preterm birth was observed in 14% of hypertensive mothers. It was found that 20% of newborns from hypertensive mothers were hospitalized and 1.5% died, while only 8% of newborns from normotensive mothers were hospitalized and 0.7% died. Thus, children born to gestational hypertension presented more clinical complications in the first year of life, requiring hospitalization. These data suggest that a hypertensive environment by itself might induce a susceptibility to neonates, regardless of the severity of the hypertensive disease [53].

Pathophysiology of preeclampsia

Preeclampsia is characterized by impaired cytotrophoblast transformation toward extravillous trophoblasts that result in reduced invasion into the maternal vascular bed [54, 55]. This phenomenon leads to reduce trophoblastic invasion into maternal spiral vessels preventing their transformation into capacitance vessels. This, in turn, impairs maternal blood flow to the placenta and also results in high perfusion pressure in the intervillus space, generating shear stress to the trophoblast [55]. This stress damages trophoblast, leading to release of harmful molecules including oxidative stress markers, inflammatory cytokines, antiangiogenic proteins, detachment and release of cell fragments, microparticles and extracellular vesicles (EVs), among others [56-58]. These harmful elements can be transported into maternal circulation causing maternal endothelial dysfunction.

At the same time, these changes generate a vicious cycle that also affects the placental blood flow leading to further release of placental materials that adversely affect maternal endothelial function [19, 59]. Not surprisingly, harmful molecules from the placenta can also reach the fetal circulation causing endothelial dysfunction. Indeed, many reports including some from Iberoamerica groups [18, 60], have described feto-placental endothelial dysfunction accompanying preeclamptic pregnancies.

Among other harmful molecules released from the placenta, the soluble vascular endothelial growth factor receptor type 1 (sFlt-1) has received much attention in preeclampsia [61-70]. 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 [71-73].

Some reports from Iberoamerican countries contributed to elucidates part of the preeclampsia pathophysiology. For instance, the levels of antiangiogenic markers (sFlt-1 and soluble endoglin (sEng)), angiogenenic (PIGF), and oxidative marker (oxidized low density lipoprotein (ox-LDL)) in Colombian preeclamptic and healthy pregnant women were evaluated. In general, 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 [74]. 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 [75]. Similarly, high maternal circulating sFlt-1 was found in Ecuadorian women who developed preeclampsia [76].

A multicentric study was conducted in Argentina, Colombia, Peru, India, Italy, Kenya, Switzerland and Thailand, to assess the accuracy of angiogenic biomarkers as predictors of preeclampsia. This study included 5121 pregnant women with risk factors for pre-eclampsia, including nulliparity, diabetes, previous pre-eclampsia, chronic hypertension, and demonstrated that the maternal serum concentrations of angiogenic markers were significantly altered in women who subsequently developed pre-eclampsia. However, angiogenic biomarkers in the first half of pregnancy do not perform well enough to predict the later development of pre-eclampsia [77].

Along with these evidences, several other studies in Iberoamerican countries have been conducted in order to quantify plasma biomarkers in women who will develop preeclampsia. Most of them were conducted using circulating levels of sFlt-1, sEng and PIGF, and are summarized in Table 1. Additionally, other less frequent biomarkers, which have been more recently correlated with preeclampsia, were also evaluated in populational studies conducted in Iberoamerican countries, and are summarized in Table 2.

Literature regarding biomarkers in preeclampsia is vast and, unfortunately, is very common to find discrepant evidences in this field. One issue is related to the fact that preeclampsia is a heterogeneous syndrome.

For this reason, researchers are including more clinical data, and not only hypertension and proteinuria in the analysis. Just, an example recently published by Chen at al. [78]. They found specific patterns of maternal serum marker profiles according to the time of onset and fetal weight. Therefore, as a recommendation, future prospective studies measuring maternal serum analytes should continue including more clinical data in the analysis, and also they should be quantified throughout pregnancy and in the post- partum period in order to better understand the importance of biomarkers for either risk for preeclampsia, or their long-term impact on the cardiovascular health of women.

Cardiovascular diseases in women who had preeclampsia

Preeclampsia is associated with a wider range of cardiovascular risk factors [25]. Preeclampsia *per se* has been considered an independent risk factor to developing atherosclerotic plaque later in life [79]. In fact, women who had preeclampsia exhibited elevated blood pressure, HDL cholesterol levels, insulin resistance and tumor necrosis factor alpha (TNF-α) than women with prior normotensive pregnancy [79]. Additionally, positive correlation between sFlt-1 levels with intima thickness and intima-media ratio were found in preeclamptic women after one year of delivery [80], demonstrating a relation between angiogenic factors and changes in vascular structure. Then, preeclampsia is a risk factor for cardiovascular disease (CVD) for both mother and child (see below) during adulthood [12, 81-83].

For instance, women who have had preeclampsia exhibit at least two fold increased risk of stroke, while risk of death due to ischemic heart disease is eight times higher when preeclampsia occurs before 34 weeks of gestation [12]. Cardiovascular atherosclerotic events, occurring as a consequence of severe endothelial function, are also observed in women who suffered hypertensive disorders during pregnancy [9, 84]. 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, 81].

In particular, the relation of the co-occurrence of multiple pregnancy complications to CVD death risk over 5 decades was determined in a large pregnancy cohort study, enrolled in 1960s [10]. This study included 14,062 women, involving women with late onset preeclampsia and early onset preeclampsia. In the absence of other complications, preeclampsia was the strongest predictor of CVD death. Early onset preeclampsia was also associated with very high CVD mortality by age 60 [26]. Similarly, Mongraw-Chaffin et al [12] investigated the varying effects of preeclampsia on CVD death by gestational timing, in a total of 20,530 pregnancies, followed-up during 40 years. Both studies concluded that early CVD screening should include previous history of preeclampsia, even in the absence of other risk factors. Also, they indicate that a more specific classification of preeclampsia, taking into account the gestational age of the occurrence, can be used for screening and early intervention of women at highest risk for CVD.

In the last regard, imaging is an effective way to clinically follow women who underwent through hypertensive disorders during pregnancy, searching for vascular dysfunction. Women who developed preeclampsia displayed increased carotid intima-media thickness, assessed 3 months postpartum [85], and this change was still observed after 12-24 months postpartum [84]. However, wall thickness was not observed after 4 years [86], or after 10-years post-partum [87], possibly due a transient adaptive response of the vasculature.

Other vascular indexes may be evaluated by image to predict maternal outcome. As an example, the augmentation index (AI) and pulse wave velocity (PWV), which are intrinsically related to elasticity of the arterial wall, are commonly used to assess arterial stiffness. Thus, patients diagnosed with early onset preeclampsia displayed more pronounced AI and PWV after delivery [88] and were also more susceptible to develop postpartum metabolic syndrome [89] than respective controls. Indeed, augmented AI and PWV may still be observed one year after preeclampsia [90], reinforcing the concept that endothelial dysfunction is not totally restored after delivery.

Interestingly, a meta-analysis including data from 37 reports, including Iberoamerican countries, reveals that younger women with prior preeclampsia (<40 years) display a more pronounced endothelial dysfunction after at least three months, compared to older women (>40 years) [91]. Hence, it seems that there are no relations of arterial stiffness and subclinical large vessels atherosclerosis with complications during pregnancy, if they are assessed prior pregnancy [92]. Also, when arterial stiffness was assessed after long periods after delivery, it did not contribute to any additional CVD risk information at that time point [87], therefore indicating the individual impact of preeclampsia in CVD risk.

In Latin-America, a study conducted in Uruguay demonstrated elevated aortic blood pressure and wave reflections, as well as augmented elastic arteries stiffness in women with preeclampsia [93]. Also, preeclamptic women from northwest of Brazil, evaluated after 5 years of puerperium, showed increased cardiovascular risk, and this may be related to the presence of metabolic syndrome [94], which directly impairs vascular function [95]. Similarly, when patients from southeast of Brazil were studied, 41% of them displayed increased 30-year global cardiovascular risk score after one year of the occurrence of preeclampsia. Myocardial hypertrophy was found in 29% of them, which was associated with obesity and with abdominal circumference. Elevated carotid intima-medial thickness was found in 27% of patients, which positively correlated with global risk as well as with myocardial hypertrophy [96].

In Chile, a study including 217 women (average age 60), who presented coronary artery disease, described that this condition is presented earlier an more severe, in women with previous history of hypertension in pregnancy than in women with previous normotensive pregnancy [97]. Nevertheless, they also describe that odd ratio to coronary artery disease was nonsignificant when previous history of hypertension in pregnancy was considered in a multivariate analysis. This, last finding may underscore the impact of association, but might be explained due to reduced sample size.

Table 3: summarize Iberoamerican evidences about cardiovascular disease in women who had preeclampsia.

Other vascular complications in women who had preeclampsia

Vascular alteration of hypertensive disorders during pregnancy is also found in tissues like eyes as showed in patients from Rio de Janeiro-Brazil [98, 99]. In particular, persistent vasodilation and hyperperfusion of the orbital territory where found in ophthalmic arteries 90 days after delivery in preeclamptic women from Minas Gerais-Brazil [100]. Also, lower vision-related quality of life was reported after 10 years of preeclamptic pregnancy, occurring simultaneously with cerebral white matter lesions [101]. These evidences show that vision impairment after hypertensive disorders during pregnancy may constitute a consequence of both alterations in local vasculature and changes in central neuron system.

Hence, preeclamptic women frequently display lesions in white matter lesions, which correspond to the occipitoparietal edema distribution, observed in reversible encephalopathy syndrome [102] and these lesions are observed even three to six years after preeclamptic pregnancy [103, 104]. Indeed, white matter lesions is independently associated with current hypertension or with a history of early-onset preeclampsia [104]. Therefore, hypertensive disorders during pregnancy might be considered an important risk marker for early cerebrovascular damage. These evidences are supported by a meta-analysis demonstrating that women with previous history of hypertensive disorders during pregnancy displayed increased chances to develop cerebrovascular disease [105]. Other neurological implication of preeclampsia is the impaired cardiovascular autonomic regulation, which begins during pregnancy and may persist after delivery. We would like to refer to review recently published by Logue and colleagues and references within in [106].

Preeclampsia has been also related to substantially increased risk for having kidney disease [107]. Patients who died from preeclampsia had prominent characteristic glomerular lesions, along with a significant increase in intraglomerular cell proliferation and activated parietal epithelial cells on a podocyte location [108]. Also, it has been found persistent urinary podocyte loss after preeclamptic pregnancies, even when angiogenic markers are unchanged [109]. Then, this feature may constitute an important marker of ongoing, subclinical renal injury. This last comment is relevant, considering that quantification of microalbuminuria in women who underwent to a preeclamptic pregnancy is controversial. Thus, while some earlier studies demonstrated a high risk of microalbuminuria after a preeclamptic pregnancy [110-114], other recent population-based study found that preeclampsia was not associated with increased risk of persisting microalbuminuria [115]. Nevertheless, in this last study, preterm preeclampsia was associated with high normal glomerular filtration rate. Also, it was found that previous preeclampsia does not seem to be a risk marker for progression to end-stage renal disease [116], demonstrating controversy in this field and reinforcing the necessity of further studies relating kidney injury after preeclampsia.

On the other hand, Bellamy et al [117] perform a systematic review and meta-analysis to quantify the risk of future cardiovascular diseases, cancer and mortality after pre-eclampsia finding no association.

Cardiovascular adverse outcomes in the offspring born to preeclampsia

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, 5, 82, 118-121]. These studies were reviewed in a recent meta-analysis, which concluded that offspring born from preeclamptic women had ~2 mmHg greater systolic and ~1.3 mmHg greater diastolic blood pressure than individuals born from normotensive pregnancies [82]. Also, Kajantie and co-workers [122] showed more evidence pointing to the association between preeclampsia and cardiovascular events in a study in a large population of preeclamptic pregnancies. The authors followed subjects born from 6410 single-fetal pregnancies, attended at two maternal Hospital in Helsinki, between 1934 and 1944. They evaluated the incidence of coronary disease, arterial hypertension and stroke between 1971 and 2003. They did not find differences in coronary heart disease incidence, but arterial hypertension was more frequently found 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.

Exposition to maternal preeclampsia was associated with greater relative wall thickness and smaller left ventricular end-diastolic volume in their children [123]. This effect could be early signs of concentric remodeling and affect future cardiac function as well as risk of cardiovascular disease in offspring from preeclampsia.

Vascular alterations in offspring born to preeclampsia were found in the analysis of childhood retinal arteriolar and venular calibers at the age of 6 years. Thus, higher maternal systolic and diastolic blood pressures in early pregnancy were associated with childhood retinal arteriolar narrowing. While, higher maternal systolic blood pressure in late pregnancy was associated with childhood narrower retinal venular caliber [124]. Complementarily, Yu et al [125] found that despite, offspring born after hypertensive pregnancy had similar microvessel density to those born after a normotensive pregnancy at birth; it was changed after the first 3 postnatal months, when they found that offspring born after hypertensive pregnancy had ~2-fold greater reduction in total vessel density [125].

Offspring from preeclamptic women may have abnormal blood perfusion in the brain. Thus, brain structural and vascular anatomy data from 7 to 10 years-old offspring from preeclamptic pregnancies demonstrated increased brain regional volumes of cerebellum, temporal lobe, brain stem and amygdalae, whereas reduced cerebral vessel radii in the occipital and parietal lobes were observed [126]. 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 the brain function of those children. This fact may also contribute to increased stroke risk to this young population in later life [127, 128].

Despite of the high incidence of preeclampsia in Iberoamerica and the Caribbean, there are insufficient studies to elucidate the long-term effects of this disease in the adulthood of the offspring. In this regard, Jayet et al. evaluated 48 children of pregnant women with preeclampsia and compared them with 90 children born of normal pregnancies, who have lived all their life at 3600 meters 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 indicate that preeclampsia affects vascular functions in offspring from preeclamptic pregnancies [21, 129].

Other studies have described an increased risk for metabolic and endocrine disease [118, 119], depression [130], cerebral palsy [131], poor cognitive outcome [132], or intellectual disabilities [133] in children born from preeclamptic pregnancies compared to non-exposed children. Also, preeclampsia is an independent predictor of low cognitive scores in preterm infants [134]. Table 4. summarize evidences about cardiovascular and non-cardiovascular diseases in children born to preeclampsia.

Vascular/endothelial dysfunction in preeclampsia: is the same in mother and offspring?

This question remains unsolved. But, an excellent work by Yu et al [125] found that offspring born after hypertensive pregnancy had ~2-fold greater reduction in total vessel density. Interestingly, this phenomenon was associated with reduced vasculogenic capacity of the human umbilical vein endothelial cells of the infant at birth, and it was proportional to levels of antiangiogenic factors in the maternal circulation [125]. Then, circulating anti-angiogenic profile found in mothers with preeclampsia impairs angiogenic capacity in their children.

Nevertheless, lower levels of PIGF during second semester of pregnancy were associated with narrower childhood retinal arteriolar caliber. However, this association was not explained by maternal blood pressure levels [135], but may be also related by the children's blood pressure [136]. Then, similarly to Yu's group work, the last study suggests that angiogenic factors from the mother may have an independent impact on vascular development, at least in the eye.

Cause of vascular dysfunction in the three compartments; mother, placenta, fetus, are not well understood. But, since reduction in microvascular density in offspring of preeclampsia was predicted by alteration in the tube formation capacity of umbilical vein endothelial cells, as well as level of angiogenic factors in the maternal circulation around the time of birth [125], it might indicate that the offspring is responding rather than causing vascular alterations in the other two compartments.

Forward-thinking cellular mechanism of endothelial dysfunction in preeclampsia

Several mechanisms for vascular/endothelial dysfunction have been studied since Roberts et al, proposed this phenomenon as the underling alteration in preeclampsia in 1989 [16]. This concept was expanded to fetoplacental circulation, offspring, and it is suggested as one of the main mechanisms linked with future cardiovascular risk in mother and her children. Also, these mechanisms have been also linked with other pregnancy disease such as gestational diabetes, intrauterine growth restriction, preterm delivery among others. Therefore, information in this field is enormous.

Nevertheless, similar endothelial dysfunction mechanisms in mother and offspring from preeclampsia may constitute only a matter of focus of research. In Figure 2, a cartoon is presented with information regarding plasma biomarkers measured in maternal and fetal side in preeclamptic pregnancies, and excellent recent reviews in this topic are referred here [7-9, 91, 137-139].

Here, some of the emerging mechanisms currently described in this field are highlight. For instance, the role of mitochondrial DNA (mtDNA) is being suggested as a contributor to vascular dysfunction in preeclampsia. mtDNA, which are potent immunological activators due to the bacterial ancestry of mitochondria, are released as a result of cell death, and may induce vascular changes and predispose to cardiovascular disease [140]. Recent evidences show that mitochondrial DNA (mtDNA), released from necrotic trophoblastic cells activate immune system via Toll-like receptor 9 (TLR9), activating protein kinases (MAPK) and potentiating the release of pro-inflammatory cytokines, ending in systemic vascular dysfunction and generation of preeclampsia-like symptoms [141]. 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 [142]. These idea are supported by the fact that, many preeclamptic women exhibit necrotic placentas [143] and emerging evidences of elevated circulating mitDNA in preeclampsia was recently revised [144].

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 a relevant issue since most of the energy of endothelial cells comes from glycolysis [145]. In preeclampsia, inactivation of glucose-6-phosphate dehydrogenase (G6PD), a rate-limiting enzyme in glucose metabolism, occurs in the fetal circulation, a phenomenon associated with the vascular dysfunction and oxidative stress observed in this disease [146]. Similarly, reduced transport and/or metabolism of other bioactive molecules such as adenosine or L-arginine [147], or metabolism of other sources of energy such as fatty acids [148], might also contribute to the metabolic alterations leading to endothelial dysfunction in preeclampsia.

In Iberoamerican countries, Julian et al [149] have described in a small group of Andean males (18-25 years) living in La Paz, Bolivia, that men whose mother had pregnancy complicated with hypertension exhibited at least six genome-wide significant methylated genomic regions (DMR), compared to control subjects. 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). Since, several genes with potential modulatory role in vascular function are included in these genes, which in turn showed an specific pattern of hypo or hyper methylation; they found that *ARID1B* gene expression was impaired in offspring from preeclampsia ($p = 0.025$), while *CTHRC1* tended to be higher ($p = 0.08$) and *SMOC2* was equivalent between groups. Therefore, they not only confirm that epigenetic mechanism are involved in vascular risk in offspring from preeclamptic preganancies, but also introduce novel target for future research.

Genetic studies have associated single nucleotide polymorphisms (SNP) in genes encoding nitric oxide synthase, but the results have not always been 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 analyzed in various groups of women from Iberoamerican. Colombian women homozygous for the Asp298 allele, in addition to the presence of a high-risk Asp298–786C-4b haplotype, were associated with the presence of preeclampsia [150]. In Maya mestizo women homozygous for the Asp298 allele also showed an association with preeclampsia but the haplotype -786C-4b-Asp298 was a better genetic marker in this population [151]. In Brazilian women with preeclampsia Sandrim et al, did not find significant differences in genotype distribution of the three polymorphisms in preeclampsia and healthy women [152]. 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 [153].

Need for actions in Iberoamerican countries

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Individual contributions

This work was carried out as a full collaboration among all the authors. CE defined the research topic.. All authors approvved the final version of the manuscript.

Disclosures

None

Tables legends

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

Table 2. Summary of information regarding other biomarkers found in population studies of preeclampsia in Iberoamerican

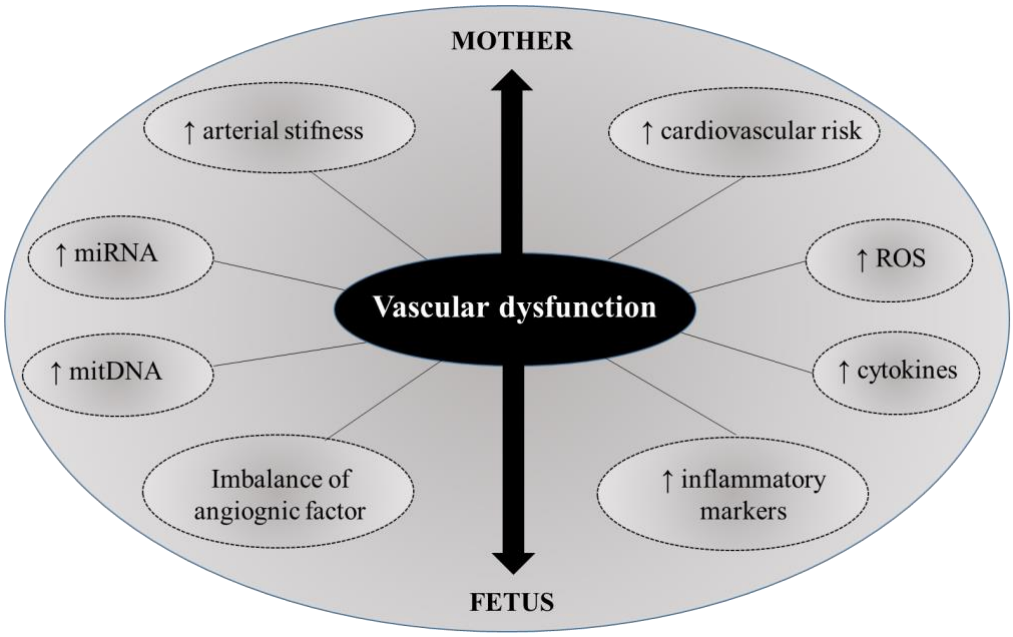
Table 3: Summary of Iberoamerican evidences about cardiovascular disease in women who had preeclampsia. (Dr. Martha Viana team)

Table 4. Summary of evidences about cardiovascular and non-cardiovascular diseases in children born to preeclampsia

Figure legends

Figure 1. Rate of preeclampsia and cardiovascular disease in Iberoamerica.

Figure 2. Plasma biomarkers measured in maternal and fetal side in preeclamptic pregnancies.



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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 hours apart.
○ The SBP or the DBP ≥ 160/110 mmHg, confirmed within a short interval (minutes)
and
○ Proteinuria ≥ 300 mg /24 hours 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/microliter (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

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

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.	[154]
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.	[155]
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.	[76]
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.	[156]
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.	[157]
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.	[77]
Brazil	20–37 weeks	Case-control	34 early PE, 26 late PE and 60 controls.	sEng is increased in the plasma from PE women.	[158]
Haiti	After 34 weeks, pre-delivery	Case-control	35 PE and 43 controls.	Increased sFlt-1 and lower PIGF levels in PE women.	[159]
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.	[160]

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	[161].
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.	[162]
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.	[163]
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.	[74]
Colombia	Not informed	Case-control	604 PE and 691 controls.	sFlt-1 was increased, and PIGF was reduced, in PE. Increased PIGF levels above 75pg/mL were found to be a protective factor for the development of PE and HELLP syndrome.	[164]
Chile	Early 6-15 weeks; and midtrimester 20-25 weeks	Cohort study	62 PE and 150 control.	PIGF decreases, whereas sEng increases, both in early and midtrimester of preeclamptic pregnancies, suggesting that the PIGF/sEng ratio might works as an excellent predictive marker of early-onset preeclampsia.	[165].
Ecuador	At delivery	Case-control	29 PE and 29 controls.	Higher plasma sFlt-1 and sEng, and lower IL-8.	[166]

Abbreviations: CRP: c-reactive protein; FGR: fetal growth restriction; GH: Gestacional hypertension; HELLP: haemolysis, 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: triglicerides; VLDL: very low density lipoprotein.

Table 2. Summary of information regarding other biomarkers found in population studies of preeclampsia in Iberoamerican

Biomarker	Country	Gestational age	Study	Sample size	Finding in preeclampsia	Reference
Adenosine deaminase (ADA)	Brazil	34-35 weeks	Prospective	60 PE, 30 controls and 20 non-pregnant.	Elevated ADA level, IL-1β, TNF-α and NF-Kb.	[167]
Adipsin	Colombia	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.	[168]
Brain-derived neurotrophic factor (BDNF)	Brazil	20-38 weeks	Case-control	38 PE and 20 controls.	Lower BDNF plasma and cross talk between BDNF and anexin-1.	[169]
c-reactive protein (hsCRP)	Ecuador	16 – 40 weeks	Prospective	24 PE and 183 controls.	High sensitive hsCRP are augmented during preeclampsia.	[170]
Cystatin C and Clusterin	Mexico	12, 16 and 20 weeks	Cohort study	15 PE and 45 controls.	Urinary cystein C and clusterin showed predictive value for PE development	[171]
Endocanabinoid system	Argentina	At delivery Placenta	Case-control	14 PE and 14 controls.	Narachidonoyl phosphatidylethanolamine phospholipase D (NAPE-PLD) expression was increased, whereas fatty acid amide hydrolase (FAAH) was decreased, in PE. No differences in cannabinoid receptor 1 (CB1) were found.	[172]
Glucose tolerance tests (OGTT)	Chile	22 -25 weeks	Retrospective	84 PE and 1690 controls.	High 2-hour glucose during the second trimester of pregnancy in women who subsequently developed PE, between 35 and 37 weeks of gestation.	[173]
Matrix metalloproteinases (MMP)	Mexico	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.	[174]

	Brazil	20 weeks and 12 weeks after delivery	Case-conrol	130 PE, 130 GH and 130 controls.	Plasma MMP-2 and TIMP-2 are enhanced in PE women.	[175]
Meteorin (METRN)	Colombia	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.	[176]
2-methoxyestradiol (2-ME)	Chile	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.	[177]
Podocalyxin	Paraguay	21 – 42 weeks	Prospective	25 PE ad 38 controls.	Higher levels of urinary podocalyxin, which was normalized after delivery.	[178]
$Na^{(+)}/H^{(+)}$ exchanger isoform 3 (NHE-3)	Argentina	At delivery Placenta	Case-control	10 PE and 10 controls.	NHE-3 expresion is decreased in PE women.	[179]
Thiobarbituric acid-reactive substances (TBARS)	Chile	At the moment of diagnosis and 30 and 120 days after delivery	Case-control	19 moderate PE, 25 sevee PE and 30 controls.	High levels of TBARS and lower levels of total antioxidant capacity and enzymatic antioxidants in mother and newborns.	[180]
Tissue factor (F3) and thrombomodulin (THBD)	Colombia	At delivery Placenta	Case-control	16 PE and 19 controls.	Increased placental levels of F3 and THBD along with infarction and hyperplasia of syncytiotrophoblast.	[181]

Abbreviations: 2-ME: 2-methoxyestradiol; ADA: Adenosine deaminase; BDNF: Brain-derived neurotrophic factor; FAAH: fatty acid amide hydrolase; GH: Gestacional hypertension; hsCRP: c-reactive protein; IL-1β; interleukin 1 beta; METRN: Meteorin; MMP: Matrix metalloproteinases; NAPE-PLD: phosphatidylethanolamine phospholipase D; NF-Kb: 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.

Table 3: Summary of Iberoamerican evidences about cardiovascular disease in women who had preeclampsia. (Dr. Martha Viana team)

Country	Study	Sample size	Finding in preeclampsia	Reference
Uruguay	Case-control	7PE, 13 healthy pregnant, 6 non-preteinuric hypertensive women, 32 non-pregnant	Elevated aortic blood pressure and wave reflections, as well as augmented elastic arteries stiffness in women with preeclampsia	[93]

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

Finding in preeclampsia	Study	Sample size	Country	Reference
High risk of child to be hospitalized for any cause during the first 24 years of life.	Population study	1,618,481singleton-born children	Denmark	[182]
	Retrospective longitudinal cohort study	351 cases	Argentina	[53]
Reduction of cognitive, affecting working memory and oculomotor control	Prospective study	10 singleton-born children	USA	[183]
Small reduction in verbal abilities at age of 10	Prospective study	2601 participants	Australia	[184]
Poorer behavior	Prospective study	2804 women and their children	Australia	[185].
High risk for respiratory diseases	Population study	22264 discordant sib-pairs	Denmark	[186]
	Population study	1,077,432 singleton-born children	Denmark	[182]
		413 cases	Australia	[131]
Increase arterial hypertension coronary disease, and stroke	Cohort study	6410 cases	Finland	[122]
Systemic and pulmonary vascular dysfunction	Prospective study	138 cases	Bolivia	[21]
Metabolic diseases	Population study	1,077,432 singleton-born children	Denmark	[182]
Later depressive symptoms	Retrospective longitudinal cohort study	788 cases	Finland	[130]

Vascular alterations	Population study Prospective study	3748 cases 600 participants	Netherlands UK	[124] [125]
Low birth weight	Prospective case-control	413 cases	Australia	[131]
Malformations in nervous system, renal, limp, Cardiac, Lip/Cleft/Palate and Chromosomal.	Population study involving five WHO regions: African, the Americas, Eastern Mediterranean, South-East Asia and Western Pacific Region	310 401 live birth	29 countries including Argentina, Brazil, Ecuador, Mexico, Nicaragua, Paraguay and Peru.	[187]
Nutritional and endocrine disease	A nested case-control study	12,804 consecutive singleton deliveries 1,077,432 singleton-born children	Norway Denmark	[188] [182]