ORIGINAL ARTICLE

Preeclampsia is Preceded by Cardiovascular Function Abnormalities

La preeclampsia es precedida por alteración de la función cardiovascular

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ABSTRACT

Background: Preeclampsia (PE) is associated with changes in cardiovascular function (CVF), but whether these changes precede and persist in the clinical phase of the disease is still unknown.

Objectives: The aim of this study was to evaluate the differences in CVF at 22 weeks of pregnancy and one year after delivery in patients who developed PE vs. those with normotension (N). The association between CVF at 22 weeks of pregnancy and the development of PE was also analyzed.

Methods: A prospective study was conducted including 260 normotensive primiparous women. Routine laboratory tests, 24-hour urine protein and blood pressure (BP) were measured at 22 weeks and one year after delivery. Cardiac index (CI), systemic vascular resistance index (SVRI), and pulse wave velocity (PWV) were measured by impedance cardiography. The population was divided into three groups according to the outcome during pregnancy: G1: PE, G2: gestational hypertension (GH) and G3: N. The results are presented as mean ± SD, ANOVA and post hoc test, $p < 0.05$.

Results: Twelve patients evolved to PE, 18 to GH and 220 remained with N. In G1, CI was lower and BP, SVRI and PWV were higher than in G3 at 22 weeks of pregnancy and one year after delivery. In G2, values were always intermediate between G1 and G3. PWV and SVRI measured at 22 weeks of pregnancy resulted predictors of PE.

Conclusions: Patients who developed PE had different CVF in the early stage of pregnancy than those with normotension. The early diagnosis of those changes could predict PE and thus contribute to prevent its complications.

Key words: Preeclampsia - Cardiography, Impedance - Pulse wave analysis - Cardiovascular physiological phenomena – Hypertension

RESUMEN

Introducción: La preeclampsia (PE) se acompaña de cambios en la función cardiovascular (FCV). Sin embargo, es desconocido si los cambios preceden y persisten a la manifestación clínica de PE.

Objetivos: Evaluar las diferencias en la FCV, en la semana 22 de gestación (22sg) y un año posterior al parto (1app) en las pa¬cientes que evolucionaron a la PE vs. a la normotensión (N). También, la asociación entre la FCV en 22sg y la evolución a PE.

Material y métodos: Estudio prospectivo, que incluyó 260 primíparas normotensas. Se midió en 22sg y a 1app: laboratorio de rutina, proteinuria de 24horas, presión arterial (PA). Por cardiografía por impedancia: índice cardíaco (IC) y de resistencia vascular sistémica (IRVS), velocidad de onda de pulso (VOP). Se formaron 3 grupos según la evolución a: PE, G1, HTA gestacional (HG) G2, y N, G3. Los resultados se presentan como media ± DS, ANOVA y test post hoc, $p < 0,05$.

Resultados: 12 pacientes evolucionaron a PE, 18 a HG y 220 a N. El G1 presentó en los dos tiempos de medición, valores inferiores de IC y superiores de PA, IRP y VOP comparados al G3. El G2 presentó valores intermedios entre el G1 y el G3. La VOP y el IRP en 22sg de gestación resultaron predictores de PE.

Conclusiones: Las pacientes que evolucionaron a PE presentaron en fase temprana del embarazo diferente FCV respecto a las normotensas. El diagnóstico temprano de estos cambios contribuiría a predecir la PE y prevenir sus complicaciones.

Palabras clave: Preeclampsia - Cardiografía de impedancia - Análisis de la onda de pulso – Fenómenos Fisiológicos Cardiovasculares Hipertensión arterial.

Abbreviations

ACI	Cardiac index	**N**	Normotension
CVF	Cardiovascular function	**PE**	Preeclampsia
GH	Gestational hypertension	**PWV**	Pulse wave velocity
HT	Hypertension	**SVRI**	Systemic vascular resistance index

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INTRODUCTION

Hypertensive disorders of pregnancy are one of the main causes of maternal and fetal morbidity and mortality (1) with a prevalence of 3-5%, (2) representing an important economic burden on the health care system. (3) The etiology and certain pathophysiologic mechanisms triggering preeclampsia (PE) are unknown. Changes in cardiovascular function (CVF) (4) occur before the onset of signs and symptoms of PE determining a characteristic hemodynamic profile. The early diagnosis of these changes could predict PE and thus contribute to prevent complications.

The assessment of CVF through the non-invasive measurement of isolated hemodynamic parameters during pregnancy is achieved by two diagnostic methods: echocardiography, (5) the test most widely used, and bioimpedance, less used but easy to implement, reproducible and cheaper than echocardiography. These characteristics have encouraged its use for the diagnosis of CVF abnormalities in pregnancy. (6) Arterial stiffness is also evaluated as a determinant of CVF by measuring pulse wave velocity (PWV), which is early compromised in pregnant women with PE. (7, 8) Although so far there are no publications with significant results, the rest of the physiological variables that determine CVF of pregnant women may present abnormalities in the early stages of pregnancy.

Some authors (9) describe a hemodynamic profile characterized by reduced total peripheral resistance and increased cardiac index (CI). Other authors (10) emphasize that CVF differs if PE develops after or before 22 weeks of pregnancy.

Preeclampsia is associated with greater future cardiovascular risk. (11) particularly due to endothelial dysfunction, which is a characteristic of this condition that is already present before pregnancy and after delivery. (12) It can also be inferred that early changes in CVF are due to endothelial dysfunction that characterizes this population, and increases the risk of future CV diseases. (13)

The primary endpoint of this study was thus to evaluate the differences in CVF before 22 weeks of pregnancy and one year after delivery in patients with PE compared with normotensive pregnant women.

The secondary endpoint was to determine if changes in CVF at 22 weeks of pregnancy had any association with the development of PE.

METHODS

A prospective, longitudinal study with control group was conducted in the Hypertension Section of the Department of Cardiology of Hospital Santojanni. Between February 2016 and September 2018, 260 normotensive, primiparous pregnant women referred from the Department of Obstetrics for routine cardiac evaluation were included in the analysis. The inclusion criteria were the following: primiparous women at 22 weeks of pregnancy, age between 18 and 33 years, and office blood pressure (BP) <140/90 mmHg. Pregnant women with a history of any chronic disease including type 1 or 2 diabetes, hypertension (HT), kidney disease, heart disease, abnormal routine laboratory tests on admission including 24-hour urine protein >300 mg or abnormal electrocardiogram were excluded from the study. All the assessments were performed during week 22 of pregnancy and one year after delivery.

Office BP was measured using an Omron 705 (Tokyo, Japan) electronic monitor with cuffs selected according to the arm circumference. Three blood pressure readings were obtained on two consecutive days according to the recommendations of the Argentine Consensus on Hypertension (14) and the American Heart Association (15). During the same week, routine laboratory tests (hematocrit, glucose, creatinine and uric acid levels, coagulation test and 24-hour urine protein) and an electrocardiogram were performed. Gestational hypertension (GH) was defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg. Preeclampsia was defined as SBP ≥140 mmHg or DBP ≥90 mmHg plus 24-hour proteinuria. The evaluation of CVF included assessments of BP, heart rate, CI, systemic vascular resistance index (SVRI) measured by impedance cardiography and arterial stiffness measured by PWV with an Aortic® device.

Impedance cardiography

Hemodynamic parameters as stroke volume, cardiac output, peripheral resistance and CI were calculated by means of impedance cardiography with a Z–Logic device (Exxer, Buenos Aires, Argentina), using the classical Kubicek equation (16).

All measurements were made in supine position, after 15 minutes of rest in a quiet environment. After recording BP, a low voltage/high amplitude sinusoidal current was introduced through two circumferential electrodes placed on the forehead and around the abdomen (outer sensors).

The thoracic impedance (Z) to the passage of the electrical current is automatically calculated by the difference between the introduced voltage and that sensed by two other electrodes placed in the neck and in the xiphoid region (inner sensors). During a short period of apnea, simultaneous recordings of the first time derivative were made, reflecting the changes during the cardiac cycle (dZ/dT) and the phonocardiogram.

The following formula was used for stroke volume calculation in milliliters,: stroke volume = p (L/Z0)2 T(dZ/dT) max, where p is the electrical blood resistivity at 100 kHz (Ω/cm), L is the mean distance between the inner electrodes (cm), Z0 is mean thoracic impedance (Ω), (dZ/dt)max is the peak value of the first derivative of thoracic impedance occurring during ventricular ejection (Ω/s), and T is ventricular ejection time (s).

Heart rate (beats/min) during cardiography was obtained from the interbeat interval. Cardiac output (CO) was calculated by multiplying stroke volume by heart rate and CI as CO/BSA (body surface area). Assuming a mean right atrial pressure of 4 mm Hg, systemic vascular resistance (SVR) was calculated with the classical formula:
SVR = [(mean blood pressure-4) / cardiac output] x 80, where 80 was used to convert the SVR from arbitrary units (mmHg×L-1×min) into the international metric system (dynes×s×cm-5), and SVRI was calculated as SVR/BSA. The method was previously tested in 15 randomly selected pregnant women. Comparisons were made 3 to 10 days later and were analyzed by a single reader, who presented a coefficient of variation of 3% ± 2.3.

Pulse wave velocity (PWV)

Pulse wave velocity was measured with a validated device (Aortic, Exxer, Buenos Aires, Argentina) (17) which uses simultaneous pressure signals allowing PWV determination in one step, given that two piezo-electric sensors simultaneously record PWV at the neck and the groin. Transit time between both wave feet are then calculated in milliseconds, using the foot-to-foot method.

Pulse wave velocity was always recorded on the right side of the patients in supine position. Two expert physicians performed the measurements. The distances between the carotid artery to the sternal notch and from there to the femoral artery were recorded, introducing the values into the equipment software. The carotid-sternal notch distance was subtracted from the carotid-femoral distance.

The carotid-sternal notch distance was measured with a flexible and inextensible metallic measuring tape, whereas the sternal notch-femoral distance was measured using a pediatric anthropometer to avoid a possible source of bias due to large bust or large abdominal circumference.

Statistical analysis

The results are presented as mean ± SD. Continuous variables with normal distribution were compared using ANOVA and Turkey's test, while those variables with non-gaussian distribution were analyzed with the Kruskal-Wallis test and Dunn's test.

A stepwise multivariate analysis was performed to evaluate the association of variables, using the development of PE as dependent variable and age, body mass index (BMI), PWV, SVRI, CI and heart rate as independent variables. Those variables with significant association ($p < 0.05$) underwent logistic regression analysis.

Statistical analysis was performed using SPSS 17.0 statistical package for Windows (SPSS Inc., Chicago, III, USA). A two-tailed p value ≤0.05 was considered statistically significant.

Ethical considerations

The study protocol was revised and approved by the local Ethics Committee.

RESULTS

The population was divided into three groups according to the outcome during pregnancy: PE, GH or normotension (N). Of the 260 patients included, 10 were excluded due to unsatisfactory measurements. Among the remaining 250 patients, 12 developed PE after 34 weeks of pregnancy, 18 developed GH between 32 and 40 weeks of pregnancy and 220 had N.

One year after delivery, two patients from the group with GH and one patient of the PE group presented chronic HT, and the rest remained with N; 12 patients of the latter group could not be contacted. Blood pressure, impedance cardiography and PWV were measured in these 238 patients. Age and BMI were similar in the three groups (Table 1).

Patients with PE presented higher values of BP, SVRI and PWV and lower CI and heart rate compared with women in the N group at 22 weeks of pregnancy and one year after delivery. In the group pf patients with GH, values were always intermediate between

Table 1. Characteristics of the population at 22 weeks of pregnancy

Variable	PE N=12	GH N=18	N N=220	ANOVA p
Age, years	27 ± 5	26 ± 4	26 ± 5	0.60
BMI, kg/m2	26 ± 3.5	25 ± 3.5	24.4 ± 5.9	0.30

PE: Preeclampsia GH: Gestational hypertension N: Normotensión. BMI: Body mass index. Values are expressed as mean ± SD,

those in the PE and N groups (Table 2).

Newborn weight of mothers in the PE group was significantly lower (2416 ± 322 g) compared with newborns of mothers with GH (3,597 ± 727 g) and N (3,597 ± 727 g); p=0.01. These results are similar to those reported by other related publications. (18)

Logistic regression analysis identified PWV and SVRI as PE predictors (Table 3).

DISCUSSION

Our study demonstrates that in patients who developed PE, CVF abnormalities preceded the development of HT.

Normal gestation (19) is characterized by a large reduction in uterine artery resistance in response to trophoblastic invasion and an increase in endothelium-dependent vasodilation that reduce total peripheral resistance by 30%. This is compensated by 40% increase in cardiac output which reaches a maximum at 28 weeks of pregnancy due to increased stroke volume and heart rate.

Blood pressure decreases below previous values during the first trimester of pregnancy. These compensatory physiological changes do not occur in PE, therefore, CVF is early impaired in pregnancy and remains asymptomatic until the second half of pregnancy when it is finally expressed as HT and proteinuria.

A generalized vasoconstriction with volume depletion occurs before PE develops due to the early endothelial dysfunction that occurs in these patients. These pathophysiological mechanisms would explain the lower CI and greater SVRI and PWV at 22 weeks of pregnancy that women with PE presented in our study compared with the N group.

One year after delivery, patients who developed PE continued with a similar trend of increased vasoconstriction compared with those with N, expressed by increased SVRI and PWV. This behavior emphasizes the hypothesis that the pathophysiological mechanisms responsible for vasoconstriction are latent before and after pregnancy, due to a strong maternal predisposition and placental dysfunction combined with pre-existing endothelial dysfunction.

These concepts are confirmed by Foo et al. (21) who recruited 356 patients intending to conceive, in whom CI and SVRI were measured a short time before pregnancy. Using this study design, they concluded that in healthy women, an early abnormal hemody-

Variables 22 weeks of pregnancy	PE N=12	GH N=18	N N=220	ANOVA p
SBP, mmHg	128 ± 10	120 ± 9	107 ±10	0.001*
DBP, mmHg	84 ± 6	75 ± 7	66 ± 6	0.001*
HR, beats/min	74 ± 10	80 ± 6	83 ± 6	0.01**
PWV, m/seg	10 ± 1.1	7 ± 0.8	5.6 ± 1	0.02*
CI, l/m/m^2	2.7 ± 0.4	3.1 ± 0.4	3.4 ± 0.6	0.01**
SVRI, din×s× cm-5/m^2	1.994 ± 151	1.683 ± 454	1.431±252	0.01*
Variables 1 year after delivery	PE N=12	GH N=18	N N=208	ANOVA p
SBP, mmHg	130 ± 11	117 ± 10	114± 8	0.01**
DBP, mmHg	79 ± 7	71 ± 7	70 ± 6	0.01**
HR, beats/min	68 ± 10	79 ± 8	81 ± 6	0.05**
PWV, m/seg	9 ± 1.3	6.4 ± 1	4.7 ± 2.6	0.01**
CI, l/m/m^2	2.4 ± 0.6	2.9 ± 0.3	3.2± 0.6	0.01**
SVRI, din×s×cm-5/m^2	1.900± 436	1.657 ± 436	1.385± 248	0.01*

Table 2. Results of cardiovascular function during pregnancy and one year after delivery

PE: Preeclampsia GH: Gestational hypertension N: Normotensión. SBP: Systolic blood pressure. DBP: Diastolic blood pressure. HR: Heart rate. PWV: Pulse wave velocity CI: Cardiac index SVRI; Systemic vascular resistance index.

Independent variables	B coefficient	Standard error	Chi-square	P
PWV, m/seg	1.1	0.6	3.3	0,02
SVRI, din×s×cm-5/m^2	1.0	0.3	2.9	0,05

Table 3. Predictors of preeclamsia at 22 weeks of pregnancy

PWV: Pulse wave velocity SVRI; Systemic vascular resistance index; B: Regression coefficient.
The table shows that SVRI and PWV resulted predictors of preeclampsia

namic profile was associated with the subsequent development of PE or fetal growth restriction, and that these abnormalities could be due to dysregulation of angiogenic and oxidative maternal factors.

The normal cutoff values for CI and SVRI obtained by impedance cardiography have not been established yet. However, most publications (22) describe significant differences between low-risk and high-risk populations, which is consistent with our results.

The classification of the hypertensive disorders of pregnancy are defined by the moment HT develops, the presence or absence of proteinuria or other symptoms indicating target organ damage (23).

However, elevated peripheral BP is only one of the variables that determine maternal CVF; therefore, a better understanding of the impairment of other hemodynamic variables would contribute to a better classification of the different types of GH, which, in turn, would help to prevent its possible complications and the appropriate choice of antihypertensive medication. (4)

Cardiovascular function abnormalities in the preclinical stage of PE have been previously described in different clinical studies. (24) Although the results are heterogeneous, the differences in the risk for PE in the population included and the different weeks of pregnancy in which CVF was measured explain this discordance.

The first studies (9) showed hyperdynamic circulation (increased CI and normal or decreased SVRI) in the preclinical phase of PE as a consequence of sympa-thetic overactivity, with a subsequent hemodynamic crossover to low CI and high SVRI coinciding with the onset of the clinical manifestation. However, these investigations were performed with Doppler echocardiography and not with impedance cardiography as in our study.

The concept of "early-onset PE (before 34 weeks) and late-onset PE (after 34 weeks) " appeared in 2008 (10). Early-onset PE was associated with greater incidence of complications, low CI and elevated SVRI, similarly to our patients, but with the difference that all the patients in our study developed PE after 34 weeks of pregnancy. In agreement with our results, other publications (21-25) demonstrated a hemodynamic profile characterized by low CI and elevated SVRI, independently of the moment PE developed.

Preeclampsia is a complex disease and time of pregnancy in which it occurs is one of the factors determining its severity.

Heart rate was lower in patients with PE vs. N patients; this characteristic remained similar after placental expulsion. Early sympathetic hyperactivity has been described in patients with PE that could be related with this finding.

Pulse wave velocity and SVRI on week 22 resulted predictors of PE: Therefore, it can be assumed that the evaluation of these parameters with other placental biomarkers could be useful for the early diagnosis of PE, if these results are confirmed in future research with a larger number of patients.

The main limitation of this study was the small num-

ber of patients who developed PE. Although the percentage found is consistent with the prevalence of PE in the general population; the challenge of achieving a large number of patients in pregnant women is known, except for multicenter studies. Despite the impedance cardiography device used has not been validated yet, our results could differentiate between populations at different risk and were reproducible.

CONCLUSIONS

Patients who developed PE had different CVF before the diagnosis and one year after delivery than those with normotension. These changes were lower CI and greater SVRI and PWV. The early diagnosis of these changes could predict PE and thus contribute to prevent its complications.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material)

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