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Maternal arterial stiffness in pregnancies affected by preeclampsia

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Kaihura C, Savvidou MD, Anderson JM, McEniery CM, Nicolaides KH. Maternal arterial stiffness in pregnancies affected by preeclampsia. *Am J Physiol Heart Circ Physiol* 297: H759–H764, 2009. First published May 22, 2009; doi:10.1152/ajpheart.01106.2008.—Preeclampsia (PE) is characterized by an aberrant maternal cardiovascular adaptation to pregnancy and increased cardiovascular risk later on in life. The aim of this study was to compare the maternal wave reflections and arterial stiffness in women with established PE and those with normotensive pregnancies, after systematic adjustment for known confounders. This was a cross-sectional study involving 69 normotensive, pregnant women and 54 women with established PE. Maternal wave reflection (augmentation index) and pulse wave velocity of the carotid-radial and carotid-femoral parts of the arterial tree were assessed noninvasively using applanation tonometry. The measurements were adjusted for maternal age, heart rate, mean arterial pressure, and aortic time to wave reflection and expressed as multiples of the median (MoM) of the control group. In the PE group, compared with controls, there was an increase in the median pulse wave velocity of both the carotid to femoral [1.1, interquartile rage (IQR) 1.0–1.3 MoM vs. 0.9, IQR 0.9–1.0 MoM; $P < 0.0001$] and carotid to radial (1.0, IQR 0.9–1.1 MoM vs. 0.9, IQR 0.9–1.0 MoM; $P = 0.01$) parts of the arterial tree. In contrast, there were no significant differences between the two groups in the median augmentation index (0.9, IQR 0.7–1.1 MoM vs. 1.0, IQR 0.5–1.8 MoM; $P = 0.46$). In conclusion, we found that established PE is characterized by increased maternal arterial stiffness but not altered maternal wave reflection.

pregnancy; applanation tonometry

PREECLAMPSIA (PE) affects about 2% of pregnancies and is one of the leading causes of maternal and perinatal mortality and morbidity (39). In this condition, the normal maternal cardiovascular adaptation, with increased intravascular volume, cardiac output, heart rate (HR), aortic distensibility, compliance, and a marked decrease in vascular resistance (9, 14, 30), fails (8). With the use of two-dimensional echocardiography, several studies have confirmed that PE is characterized by a marked reduction in the maternal cardiac output and increase in peripheral resistance, whereas the preclinical phase of the disease is characterized by a hyperdynamic high-output/low-resistance circulation (4, 7, 8). Despite the extensive number of studies in the maternal hemodynamic adaptation during PE, the available information on maternal central hemodynamics, wave reflection, and arterial stiffness, in this condition, is scarce.

Arterial stiffness is an independent predictor of cardiovascular events and mortality even in healthy subjects (41). Interestingly, women with a history of PE are also at an increased risk of cardiovascular events later on in life (2), and this association may be mediated by an increase in maternal arterial stiffness. A noninvasive assessment of arterial stiffness is possible by the simple, validated, and reproducible technique of applanation tonometry with which central blood pressures (BPs), arterial wave reflection, and pulse wave velocity (PWV) of different parts of the arterial tree can be studied (24, 38). Studies using applanation tonometry have demonstrated that normal pregnancy is associated with a decrease in central pressures and arterial wave reflection and no change in the PWV of the carotid-radial and carotid-femoral arterial pathways (21, 31). In contrast, longitudinal studies that assessed PWV, using pulse transducer heads, demonstrated a decrease in PWV (carotid femoral) and consequently an increase in aortic distensibility in normal pregnancy (9). Studies in women with PE or a history of PE have reported conflicting results (10, 11, 18, 20, 29, 32). This may be due to the small study populations or to the fact that a number of these studies assessed different parameters of arterial stiffness without comprehensively adjusting for all the known confounding variables such as BP and HR.

The aim of the current study was to compare the maternal arterial stiffness, assessed by arterial wave reflection and PWV, using applanation tonometry, between a large number of women affected by PE and women with normotensive pregnancies, after a systematic adjustment for all possible confounders.

MATERIALS AND METHODS

Subjects. This was a cross-sectional study involving 69 normotensive, pregnant women and 54 women with established PE. The normotensive subjects were recruited from the routine antenatal clinic. They were all healthy, free of medication, and with no family history of premature heart disease. All women had uncomplicated pregnancies and delivered fetuses of appropriate size for the gestation. The preeclamptic women were recruited from the antenatal hospital ward, where they were admitted due to PE.

The diagnosis of PE was made according to the criteria of the International Society for the Study of Hypertension in Pregnancy (6). Under this classification, PE was defined as diastolic BP of at least 110 mmHg on one occasion or diastolic BP of at least 90 mmHg on two consecutive occasions more than 4 h apart, in combination with proteinuria (≥300 mg total protein in a 24-h urine collection or, if this was not available, ≥2 proteinuria by dipstick analysis on two consecutive occasions at least 4 h apart) developing after 20 wk of gestation in previously normotensive women. In PE superimposed on chronic hypertension, significant proteinuria (as defined above) should develop after 20 wk of gestation in women with known chronic hypertension. The diagnosis of fetal growth restriction was based on the delivery of an infant with a birth weight below the 10th percentile for gestation, sex of the neonate, and maternal characteristics (12).

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Maternal age, ethnic group, smoking status, parity, body mass index, and BP were recorded. The PE group included 7 women with chronic hypertension and superimposed PE. Furthermore, within the same group, 46 women were on antihypertensive medications: 36 of them on one agent, 8 of them on two agents, and 2 of them on three agents. Overall, 22 of the treated PE women were on β-blockers. The study was approved by the Institutional Review Committee, and all women gave written, informed consent.

Arterial stiffness and wave reflection measurements. Peripheral BP was measured in the right arm using an ambulatory BP monitor (Microlife Medical 90207), which has been validated in pregnancy (28). Systolic and diastolic BPs were measured twice and averaged. Radial artery waveforms were obtained with a high-fidelity micromanometer (SPC-301; Millar Instruments, Houston, TX) from the wrist, and a corresponding central waveform was generated with a validated transfer function (Sphygmocor; AtCor Medical, Sydney, Australia) as previously described in detail (16, 25, 38). The augmentation index (AIx), a composite measure of systemic arterial stiffness and wave-reflection amplitude, and central systolic, diastolic, and pulse pressures were determined with the integrated software. Information on first systolic peak and its height (P1H), second systolic peak (P2), and aortic time to wave reflection between the start of the systolic curve and the inflection point (T_r) was also given. Mean arterial pressure (MAP) was obtained by an integration of the waveform. Aortic (carotid femoral) and brachial (carotid radial) PWV were measured as previously described (21, 38). All measurements were performed after a period of rest of at least 10 min in a left lateral position to avoid vena cava compression by the uterus. All measurements were made in duplicate, and mean values were used in the subsequent analysis. We have previously shown that the interobserver and intraobserver intraclass correlation coefficients were *1*) 0.95 and 0.97 for AIx and *2*) 0.9 and 0.9 for PWV (21). Additionally, the SphygmoCor quality control, which is incorporated within the software, was respected for each measurement.

Statistical analysis. The normality of the distribution of the data was examined with the Kolmogorov-Smirnov test. For those parameters that were not normally distributed, a logarithmic transformation was performed. Data were expressed as means ± SD or as median and interquartile range (IQR) for normally and nonnormally distributed data, respectively. Comparisons between groups were performed using unpaired Student *t*-test, Mann-Whitney *U*-test or χ^2 for numerical and categorical data, respectively. To compare the values of AIx and PWV in the two groups of women, adjusting for variables that are known determinants of them, the following three steps were taken. First, linear regression analysis was used to determine which factors among the maternal demographic (maternal age, ethnic group, parity, height, smoking, and gestational age) and vascular characteristics (HR, MAP, and aortic T_r) were significant predictors of AIx and PWV (carotid radial and carotid femoral) in the control group. Second, the distribution of AIx and PWV, expressed as multiples of the median (MoM) of the control group, were determined for the PE group. Third, a nonparametric test was used to compare the MoMs of AIx and PWV in the two groups of women examined.

The statistical analyses were performed using the Statistical Package for Social Sciences (version 12.0).

RESULTS

Recordings were successfully obtained from all women, and they all tolerated the studies well (Fig. 1). Among the 54 women who had PE, 20 women had early onset disease and had to be delivered before 34 wk of gestation due to the severity of the condition. The values of all the parameters are given for early and late PE. The demographic characteristics of the study participants are given in Table 1. When compared with normotensive controls, women with PE were more likely to be black with higher body mass index and delivered smaller babies earlier, as expected.

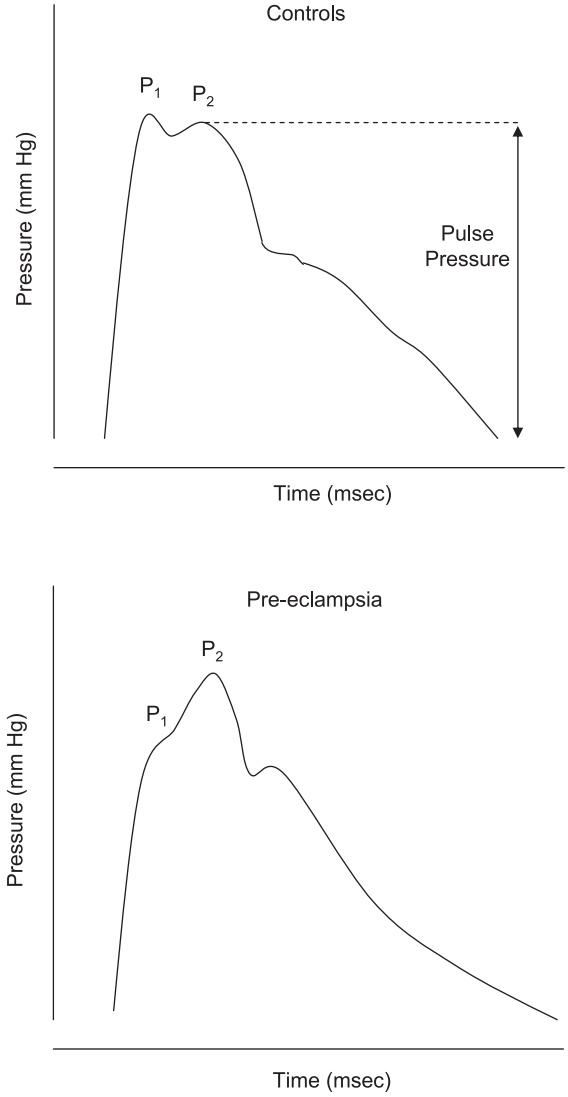

Fig. 1. Typical ascending aortic waveforms of normotensive and preeclamptic women, showing two systolic peaks (P1 and P2). Augmentation index is calculated as the difference between P2 and P1, expressed as percentage of pulse pressure.

The hemodynamic parameters are given in Table 2. When compared with normotensive women, women with PE had slower HR and longer heart cycle, which was mainly due to the longer duration of the diastole rather than the ejection duration time. By definition, all BP indexes (peripheral and central, and systolic and diastolic) were significantly higher in women with PE. Peripheral pulse pressure, a valuable surrogate measurement of arterial stiffness, was higher in women with PE. In women with PE, the height of P1 (the maximum pressure created by the forward-going pressure wave), P1H (an index of peak ventricular ejection velocity), and P2 were significantly elevated (data not shown). The increased P2 could also be explained by the shorter aortic T_r, the timing of the reflected wave, which caused a shift of the reflected wave earlier into systole.

The raw values of AIx were significantly increased in women with established PE (Table 2). The multiple regression

Table 1. *Demographic characteristics of the study populations*

Parameter	Controls	PE		*P* Value	
		Late PE	Early PE	Overall PE	Early vs. late PE
n	69	34	20		
Maternal age, yr	30.7±6	30.5±7	30.7±6.6	0.9	0.9
Ethnic group				0.02	0.01
White, *n* (%)	35 (50.7)	13 (38.2)	1 (5)		
Black, *n* (%)	28 (40.6)	16 (47.1)	17 (85)		
Others, *n* (%)	6 (8.7)	5 (14.7)	2 (10)		
Smoking, *n* (%)	15 (21.7)	7 (20.6)	2 (10)	0.4	0.3
Nulliparity, *n* (%)	43 (62.3)	21 (61.8)	9 (45)	0.4	0.2
Maternal height, m	1.6±0.05	1.6±0.06	1.6±0.05	0.98	0.5
Maternal weight, kg	75±12.6	81.8±14.4	83.6±14.5	0.003	0.6
Body mass index, kg/m^2	28±4.4	30.5±4.8	31±5.4	0.002	0.7
Gestational age at entry, days	221±36	255±12	200±23	0.02	<0.0001
Gestational age at delivery, days	281 (273–286)	262 (256–270)	210 (196–227)	<0.0001	<0.0001
Birth weight, centiles	59.6 (31.8–76)	20.4 (6.2–57.3)	1.5 (0.1–7.8)	<0.0001	<0.0001

Values are means ± SD or as median (interquartile range) for normally and nonnormally distributed data, respectively; *n*, number of patients per group. Values are given for late and early preeclampsia (PE). Comparisons were performed between normotensive women and women with PE overall and also between women with early and later onset PE (last *P* value column).

equation for AIx in the control group was as follows: AIx = 49.752 + 0.447 × maternal age − 0.630 × HR + 0.464 × MAP − 0.296 × aortic T_r (R^2 = 0.652, P < 0.0001).

For each patient and using the formula above, we calculated the expected AIx value and the ratio of the observed to expected value. The values of AIx (expressed as MoMs of the control group) were not statistically significantly different between the controls and the women with PE (1.0, IQR 0.5–1.8 MoM vs. 0.9, IQR 0.7–1.1 MoM; P = 0.46) (Fig. 2). The exclusion of women with chronic hypertension did not alter any of the above results. Furthermore, because of the known effects of β-blockers on the central pressure and HR (34), a further analysis was performed after the exclusion of the women on β-blockers, and the results were unchanged. Similarly, within the group of women with established PE, the levels of AIx were similar irrespective of the use/no use or the number of antihypertensive medications.

The PWVs (carotid femoral and carotid radial) were significantly higher in women with established PE (Table 2). The multiple regression equations for the PWVs in the control group were as follows: PWV (carotid femoral) = 1.726 + 0.063 × maternal age + 0.020 × MAP + (0.595 if Afro-Caribbean, 0 if any other group) (R^2 = 0.38, P < 0.0001). PWV (carotid radial) = 0.956 + 0.084 × maternal age + 0.047 × MAP + (0.554 if Afro-Caribbean, 0 if any other group) (R^2 = 0.28, P < 0.0001).

For each patient and using the formula above, we calculated the expected PWV value and the ratio of observed to expected

Table 2. *Vascular characteristics of the study populations*

Parameter	Controls	PE		*P* Value	
		Late PE	Early PE	Overall PE	Early vs. late PE
n	69	34	20		
Heart rate, beats/min	81±11.1	75.7±11.1	71.9±13.1	0.002	0.2
Heart cycle, ms	749.9±116.2	810.1±123	859.1±152.7	0.001	0.2
Ejection duration, ms	312.6±29.7	311±25.7	324.7±21.8	0.48	0.05
Diastole time, ms	437.3±97.4	499±105.7	534.4±138.1	<0.0001	0.2
Peripheral SBP, mmHg	114.8±10.3	138±13.3	144±16.5	<0.0001	0.1
Peripheral DBP, mmHg	69.4±7.9	88.4±7.2	91.3±10.5	<0.0001	0.2
Mean arterial pressure, mmHg	84.5±8.1	104.9±8.5	108.9±11.8	<0.0001	0.1
Peripheral PP, mmHg	45.4±7.3	49.6±9.9	52.7±10.4	0.001	0.2
Central SBP, mmHg	96.5 (89–102.2)	125.2 (120–134)	133.7 (128.6–138.3)	<0.0001	0.004
Central DBP, mmHg	68 (64–71)	89.2 (82–93)	91 (84.1–102)	<0.0001	0.06
Central PP, mmHg	27 (24.2–31.5)	36.2 (30.2–44.1)	43.5 (37.7–47.8)	<0.0001	0.19
P1H, mmHg	25 (23.5–28.7)	27.7 (24–30.5)	32 (25.7–34.3)	0.002	0.03
Aortic T_r, ms	152.5 (144.7–166)	141.5 (134.2–146.5)	136.5 (132.5–145.3)	<0.0001	0.2
SEVR, %	119.4±19.4	137.5±22.8	138.6±31.6	<0.0001	0.8
Augmentation index, %	4±13.6	23.8±9.9	25.1±11.2	<0.0001	0.6
Amplification ratio (PPP/CPP)	1.6±0.1	1.3±0.1	1.3±0.1	<0.0001	0.9
Nonaugmented amplification ratio (P1/CDBP)	1.7 (1.6–1.8)	1.7 (1.7–1.7)	1.7 (1.7–1.8)	0.17	0.4
PWV (carotid radial), m/s	7.5±1.2	9.5±1.1	9.3±0.7	<0.0001	0.4
PWV (carotid femoral), m/s	5.5±0.7	7.2±1.4	7.3±0.9	<0.0001	0.8

Values are means ± SD or as median (interquartile range) for normally and nonnormally distributed data, respectively; *n*, number of patients per group. Values are given for early and late onset PE. Comparisons were performed between normotensive women and women with PE overall and also between women with early and later onset PE (last *P* value column). SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; T_r, reflection travel time; SEVR, subendocardial viability ratio; PPP, peripheral pulse pressure; CPP, central pulse pressure; CDBP, central diastolic blood pressure; PWV, pulse wave velocity.

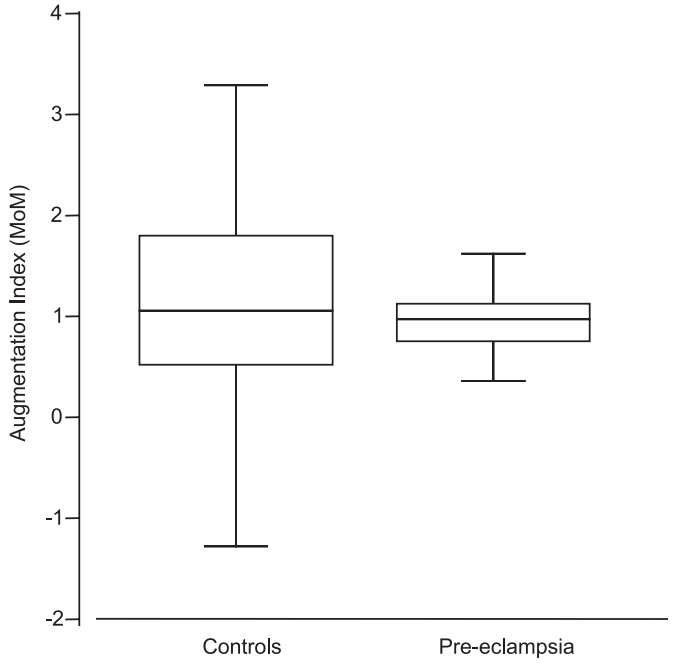

Fig. 2. Box and error bars comparing the maternal augmentation index, expressed as multiples of the median (MoM) of the control group, between normotensive controls and women with established preeclampsia ($P = 0.46$). Boxes represent interquartile range, where the line represents the median. Error bars at top and bottom of the box represent the highest and lowest values.

value. The adjusted values of PWV (carotid femoral) expressed as MoMs of the control, unaffected group were significantly elevated in women with PE compared with controls (1.1, IQR 1.0–1.3 MoM vs. 0.9, IQR 0.9–1.0 MoM; $P < 0.0001$). The results were similar for PWV (carotid radial) (1.0, IQR 0.9–1.1 MoM vs. 0.9, IQR 0.9–1.0 MoM; $P = 0.01$) (Fig. 3). The values (expressed as raw values or as MoMs of the control group) of PWV were significantly elevated in the PE group, compared with controls, even after the exclusion of the women with chronic hypertension or those on β-blockers (data not shown). Within the same group of women, the levels of PWV were similar irrespective of the use/no use or the number of antihypertensive medications (data not shown).

The AIx and PWVs were not significantly correlated with any of the hematological or biochemical markers (platelets, aspartate aminotransferase, creatinine, and proteinuria/24h) measured in women with established PE (data not shown). Additionally, in women with established PE, there was not a statistically significant difference in AIx and PWV (carotid femoral and carotid radial) between those with or without fetal growth restriction, as defined by birth weight below the 10th or the 5th centile for the gestation (data not shown).

DISCUSSION

The study has demonstrated that PE is associated with increased maternal central pressures and PWVs but not altered wave reflection, suggesting that maternal large artery stiffness in this population is increased compared with women with uncomplicated pregnancies.

Previous studies assessing maternal arterial stiffness, using applanation tonometry, in women with established PE have revealed inconsistent results, which could be due to the lack of adjustments that were performed for possible confounders of the parameter in question, the relative small number of women examined, or the severity of PE. Three studies, assessing maternal wave reflection, demonstrated a significant increase of AIx in women with established PE but without comprehensively adjusting for maternal age, BP, HR, and aortic T_r (18, 29, 32), important confounders of AIx. Conversely, Elvan-Taşpinar et al. (10) showed no difference in AIx between normotensive pregnant women and women with PE, after adjustment for determinants of AIx. One study examining PWV (carotid femoral) reported no difference between women with established PE and normotensive controls after the adjustment for MAP (10). In the current study, examining a larger

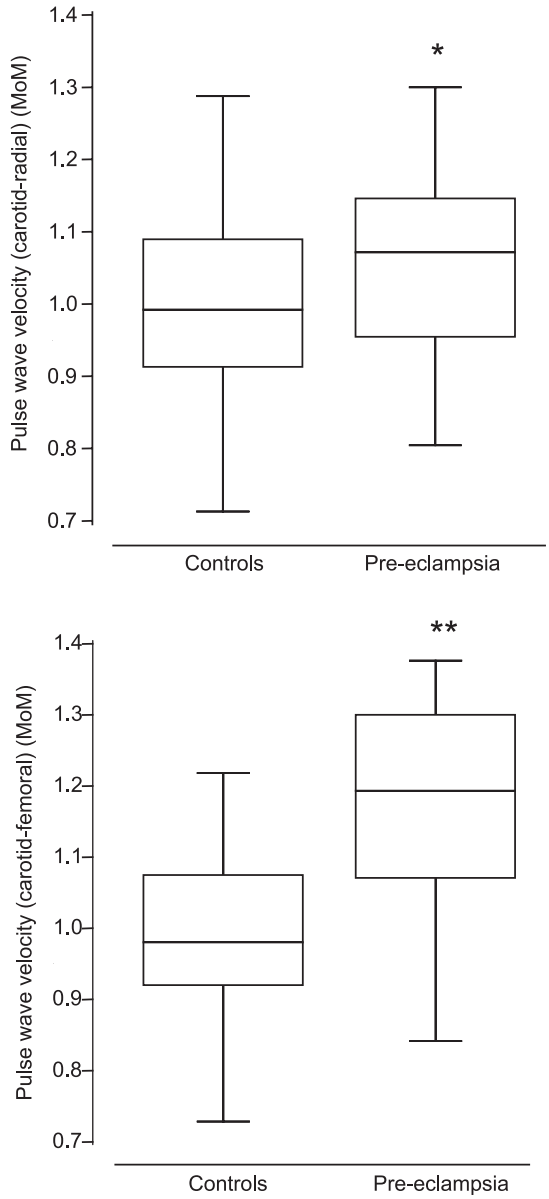

Fig. 3. Box and error bars comparing the maternal pulse wave velocity of the carotid-radial and carotid-femoral parts of the arterial tree, expressed as MoM of the control group, between normotensive controls and women with established preeclampsia (*$P = 0.01$; **$P < 0.0001$). Boxes represent interquartile range, where the line represents the median. Error bars at top and bottom of the box represent the highest and lowest values.

number of women with severe PE, we establish that PE is characterized by increased PWV, but not AIx, compared with that of normotensive pregnancy, even after adjusting for all possible confounders.

The PWV in women with established PE was 18% higher compared with that in normotensive controls. This is a big difference considering the fact that aortic PWV increases by only ~6% per decade in healthy individuals (1). Previous studies, some of them longitudinal, assessing the arterial stiffness of other vascular pathways such as base of the aorta to popliteal artery (33) and abdominal aorta (35), have also confirmed increased arterial stiffness in women with established PE. The observed increased aortic arterial stiffness could be mediated through the action of homocysteine or insulin resistance. Studies in healthy and diseased nonpregnant populations have demonstrated that PWV is strongly and positively associated with the levels of homocysteine (3, 22) and insulin resistance (13), which are also characteristics of women with established PE (15, 26). Irrespective of the exact underlying etiology, these findings suggest that large conduit arteries are involved in the aberrant hemodynamic adaptation of PE. Furthermore, studies in women with a history of PE have demonstrated increased PWV (carotid femoral) (11) and the persistence of maternal endothelial dysfunction months following the index pregnancy (5). The increased maternal arterial stiffness, observed in our study, and endothelial dysfunction (23, 40) in established PE and following a pregnancy complicated by PE (5, 11) could provide a plausible link between this condition and the increased risk of cardiovascular events that these women experience later on in life (2).

AIx refers to the difference between the second and first systolic peaks, expressed as a percentage of the aortic pulse pressure. When compared with normotensive women, women with established PE had higher first systolic peak, which provides an estimate for stroke volume, higher second systolic peak, and shorter aortic T_r, which represents an estimate of the aortic PWV. Consequently, the increased AIx observed in women with PE was due to both increases in PWV and wave reflection from the periphery with earlier return of the reflected wave as a result of increased arterial stiffness. However, when adjustments for maternal age, HR, MAP, and aortic T_r were performed, the above differences were not significant. Normally, PWV and AIx are related. The dissociation between these arterial stiffness indexes, observed in the current study, has also been widely described in other conditions such as the aging process (37), acute inflammation (36), diabetes (19), and metabolic syndrome (27), and it has been suggested that it might be due to dissipation of the energy of the incident pressure wave blunting wave reflections. Although in the present study, maternal plasma glucose levels were not measured at the time of the assessment of maternal arterial stiffness and none of the women developed gestational diabetes mellitus, it is widely accepted that metabolic syndrome characterizes women affected by PE (15) and could potentially explain the observed dissociation between AIx and PWV.

Furthermore, AIx depends on the intensity of the reflected wave, and, as such, it will depend on the diameter and elasticity of the small muscular arteries/arterioles at the major sites of pressure wave reflection. Therefore, alterations in muscular smooth muscle tone affecting mainly the small muscular arteries but not the elastic aorta might influence reflected wave intensity and hence AIx, independently of PWV. In accordance with this, different maneuvers such as the administration of vasoactive substances will affect AIx and PWV differently (17).

A limitation of our study is that this was a cross-sectional study, and, consequently, we are unable to comment whether the observed increased PWV in women with PE is the cause or the consequence of the condition. Only longitudinal studies that assess women before, during, and following pregnancy will be able to address this question.

In summary, the current data suggest that PE is associated with increased maternal large artery stiffness rather than wave reflection from sites of impedance mismatch in the periphery. Although arterial stiffening characterizes women with established PE, it is uncertain whether this is the cause or the consequence of the disease. To what extent this method can be used to identify women at risk before the development of the condition remains to be determined.

GRANTS

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