SUPPLEMENTAL MATERIAL

Data S1. Supplemental Methods

Non-Invasive Hemodynamic Assessment

In summary, all participants were asked to withhold any vasoactive medications, alcohol, tobacco, and caffeine for 12 hours prior to the study. The study was performed by three trained cardiac sonographers with patients laying supine in a darkened room with controlled temperature. For assessment of carotid-femoral pulse wave velocity (cfPWV), transit distances were obtained from body surface measurements from the carotid tonometry site to the manubrium sternum and from the manubrium sternum to the femoral artery to estimate aortic path length (*D*) according to the subtraction method. This was followed by arterial tonometry of the femoral and carotid arteries, with simultaneous ECG recording. The time (*t*) between the onset of carotid and femoral waveforms was determined as the mean of at least 10 consecutive cardiac cycles. cfPWV was calculated as *D/t* (m/s), where *D* is distance in meters and *t* is the time interval in seconds.

For pressure-volume and wave separation analyses, blood pressure was measured 3 times, 2 minutes apart, with an electronic sphygmomanometer using a cuff microphone over the right brachial artery to enhance fidelity. This was immediately followed by applanation tonometry of the right brachial artery. Average systolic and diastolic cuff pressures were used to calibrate the peak and trough of the signal-averaged brachial pressure waveform. Diastolic and integrated mean brachial pressures were then used to calibrate carotid, radial, and femoral pressure tracings obtained with arterial applanation tonometry. The carotid pressure waveform is used as a surrogate of the central aortic pressure waveform, given its immediate proximity to the aorta. To determine aortic flow, 2-dimensional Doppler echocardiography was used in left lateral decubitus to measure the left ventricular outflow tract (LVOT) diameter (parasternal long-axis view) and time velocity integral (apical long-axis view). Doppler audio was digitized online throughout these acquisitions. LVOT area was multiplied by LVOT velocity time integral to calculate aortic flow. This was immediately followed by repeat carotid tonometry in left lateral decubitus for estimation of central pressure nearly concurrently with estimation of aortic flow.

From the calibrated carotid pressure waveform, central systolic blood pressure (cSBP), central diastolic blood pressure (cDBP), and central pulse pressure (cPP) were estimated. During pressure/ flow analyses, systemic vascular resistance (SVR, representing the steady resistive load imposed by peripheral arteries and arterioles) was calculated as the impedance at zero frequency (Z_0). Aortic characteristic impedance (Z_c) represents aortic opposition to pulsatile inflow from the contracting left ventricle. Z_c was calculated in the time domain as the ratio of increase in central pressure to the corresponding increase in aortic flow in early systole. Total arterial compliance (TAC) was estimated using the diastolic area method in the last 2/3 of diastole as previously validated. We also estimated proximal aortic compliance (PAC), calculated from the Bramwell–Hill equation: $PAC = V\Delta P/\rho\Delta V$, where V is aortic volume, P is aortic pressure, and ρ is blood density. Lastly, when aortic pressure and flow are known, forward (P_f) and reflected (P_b) pressure waves can be separated, and the amplitude (peak minus trough) of each wave is assessed. Overall, these methods have been shown to be highly correlated with invasive measures and to have high reproducibility, with intraclass correlation coefficients of 0.93-0.95.[33,44]

Power estimation

Post-hoc power calculations were made for cfPWV, which is the established measure of arterial aging and the only parameter with published normative values in the population. The median cfPWV for individuals who are 35 years old (average age in our sample) is 6.29 m/s with SD of 0.937 m/s for women[33]. Using a t-test assuming a 0.5 m/s difference in cfPWV between preeclampsia and controls, and a two-sided alpha of 0.05, our sample size of 40 participant per arm was predicted to have approximately 70% power to detect a difference in cfPWV between the two groups.

Table S1. Results of multivariable linear regression models with increasing number of adjustment covariates, demonstrating the mean difference and 95% confidence interval for each hemodynamic variable between preeclampsia and control groups.

Variable	Model 1* aMD (95% CI) between PE and controls	Model 2 † aMD (95% CI) between PE and controls	Model 3 ‡ aMD (95% CI) between PE and controls
Brachial blood pressure			
SBP (mmHg)	+13.4 (7.4, 19.4) P<0.0001	+8.2 (2.2, 14.2) P=0.008	+7.2 (1.1, 13.3) P=0.021
DBP (mmHg)	+10.0 (6.1, 13.8) P<0.0001	+7.5 (3.5, 11.4) P=0.003	+6.9 (2.8, 10.9) P=0.001
MAP (mmHg)	+12.6 (8.0, 17.3) P<0.0001	+8.8 (4.1, 13.5) P=0.0004	+8.0 (3.2, 12.8) P=0.001
Central blood pressure			
Brachial PP (mmHg)	+3.5 (-1.2, 8.1) P=0.141	+0.8 (-4.1, 5.6) P=0.755	+0.4 (-4.7, 5.4) P=0.888
Central SBP (mmHg)	+17.2 (10.3, 24.1) P<0.0001	+11.2 (4.3, 18.1) P=0.002	+10.0 (3.0, 17.2) P=0.006
Central DBP (mmHg)	+10.2 (6.3, 14.1) P<0.0001	+7.6 (3.6, 11.6) P=0.0003	+7.0 (2.9, 11.01) P=0.001
Central PP (mmHg)	+7.0 (1.8, 12.2) P=0.0009	+3.6 (-1.7, 8.9) P=0.179	+3.2 (-2.4, 8.6) P=0.26
Aortic stiffness			
cfPWV (m/s)	+0.68 (0.30, 1.07) P=0.0006	+0.46 (0.06, 0.86) P=0.026	+0.42 (0.007, 0.82) P=0.047
Steady arterial load			
SVR (dyne x s/m^5)	+351.1 (192.8, 509.4) P<0.0001	+339.4 (154.1, 494.8) P<0.0001	+326.4 (170.2, 482.6) P<0.0001
Pulsatile arterial load			
Z_c, (dyne x s/m^5)	+11.1 (-11.0, 33.1) P=0.320	+0.49 (-22.9, 23.9) P=0.967	-1.82 (-26.03, 22.39) P=0.881
PAC (10^{-6} cm^4/dyne)	-1.54 (-3.14, 0.07) P=0.060	-0.64 (-2.38, 1.10) P=0.467	-0.35 (-2.13, 1.44) P=0.701
TAC (mL/mmHg)	-0.21 (-0.42, -0.0001) P=0.049	-0.16 (-0.38, 0.06) P=0.157	-0.12 (-0.35, 0.10) P=0.290
P_f (mmHg)	+2.2 (-2.2, 6.6) P=0.325	-0.9 (-5.5, 3.7) P=0.703	-1.4 (-6.2, 3.4) P=0.558
Peripheral wave reflections			
P_b (mmHg)	+2.4 (0.7, 4.1) P=0.006	+1.8 (0.2, 3.4) P=0.031	+1.8 (0.2, 3.5) P=0.033
GRC	+0.04 (0.008, 0.064)	+0.05 (0.02, 0.07)	+0.05 (0.02, 0.08)

	P=0.014	P=0.001	P=0.0004
AI_x (%)	+9.1 (+5.1, 13.1) P<0.0001	+8.9 (4.9, 12.8) P<0.0001	+8.7 (4.6, 12.8) P<.00001

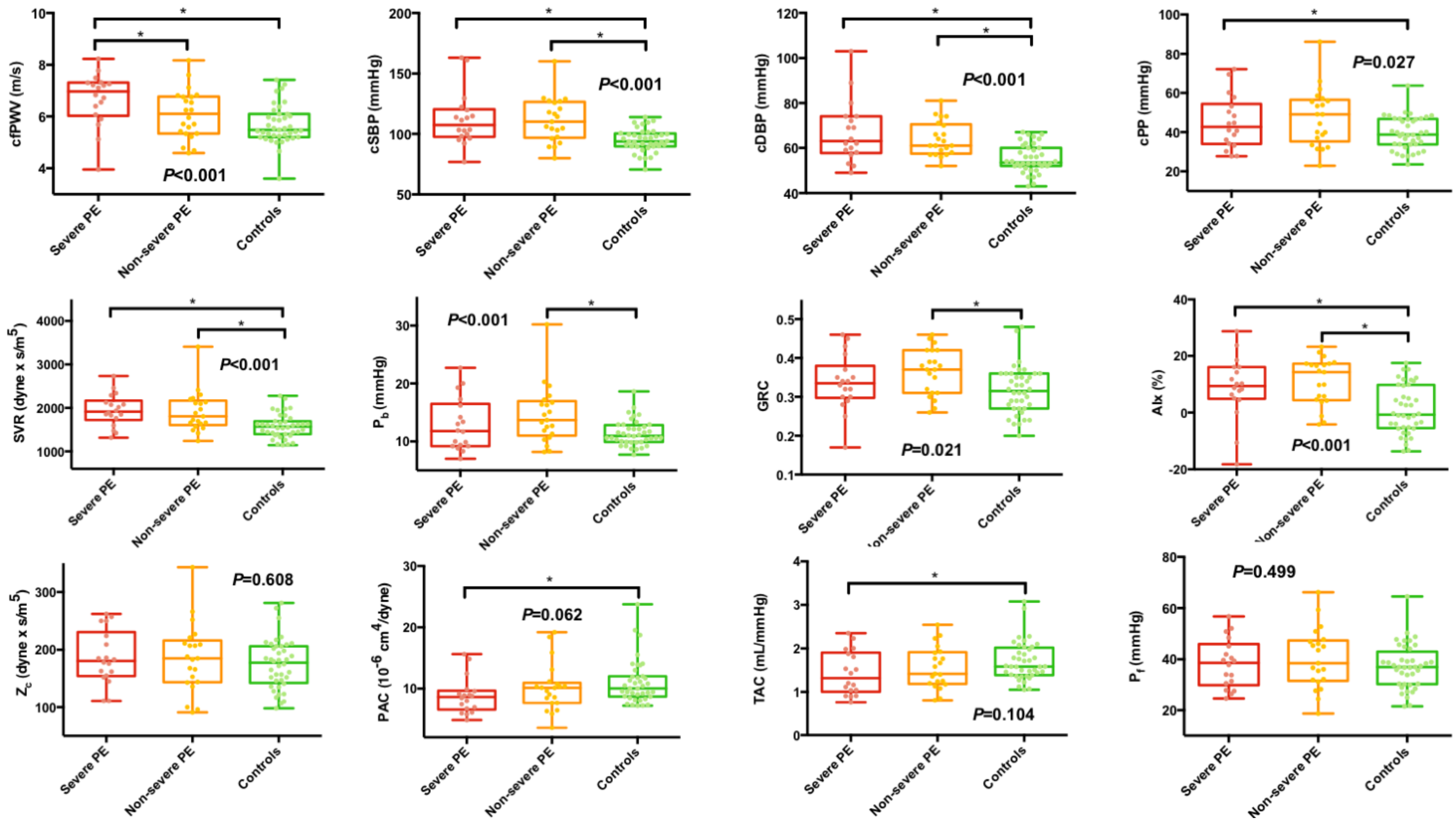
* Model 1 was adjusted for age only.

† Model 2 was adjusted for age, body mass index, serum creatinine and history of hypertension.

‡ Model 3 was adjusted for the same variables as Model 2, plus gravidity, and history of hyperlipidemia, diabetes and smoking.

AIx: augmentation index. aMD: adjusted mean difference. cfPWV: carotid-femoral pulse wave velocity. CI: confidence interval. DBP: diastolic blood pressure. GRC: global reflection coefficient. PAC: proximal aortic compliance. P_b: reflected pressure wave amplitude. PE: preeclampsia. P_f: forward pressure wave amplitude. SBP: systolic blood pressure. SVR: systemic vascular resistance. TAC: total arterial compliance. Z_c: aortic characteristic impedance.

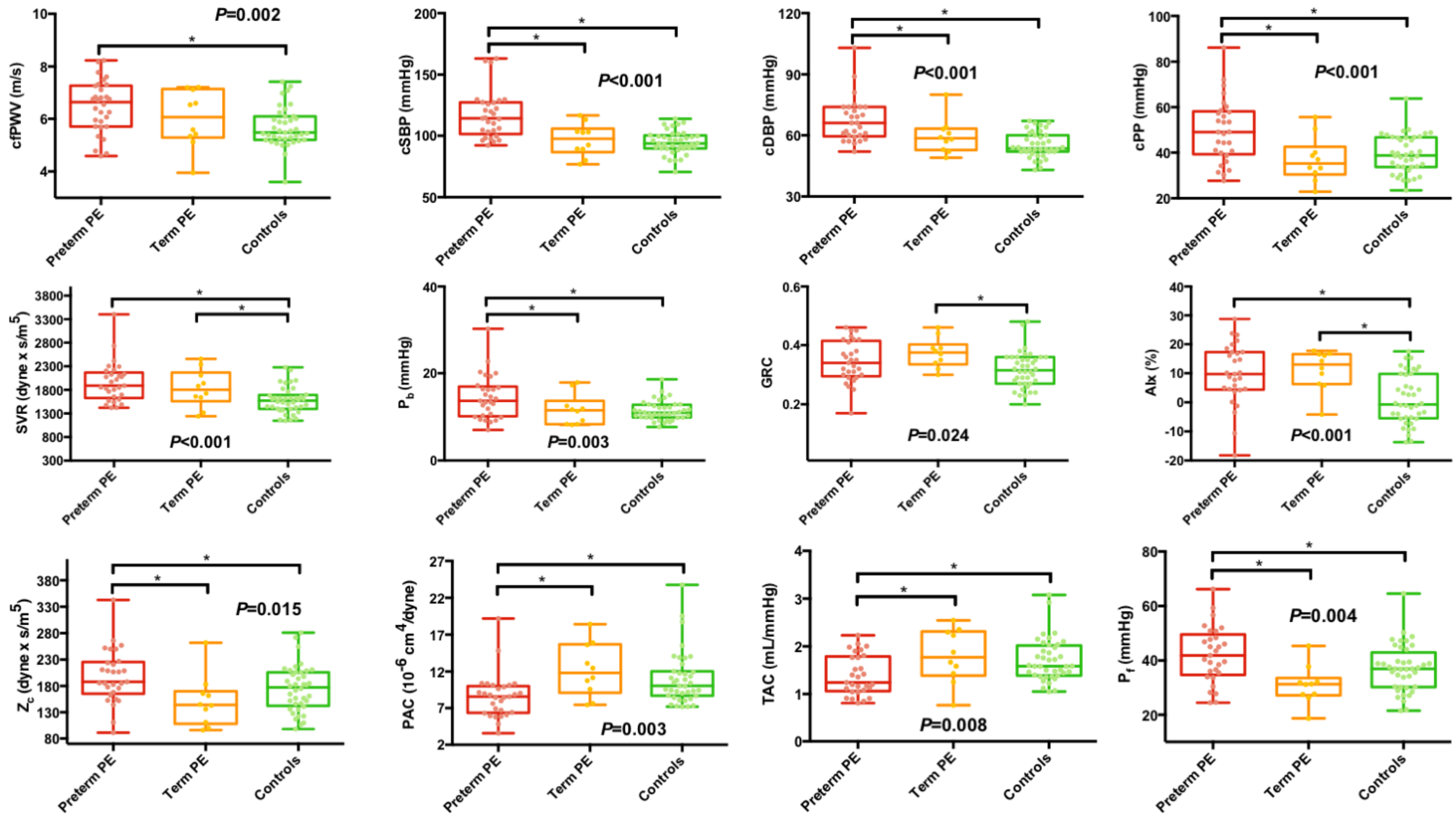
Figure S1. Unadjusted comparisons of arterial hemodynamics among women with history of severe preeclampsia, non-severe preeclampsia, and controls with previous normotensive pregnancies.



Top row: measures of aortic stiffness and central blood pressure. Middle row: measures of steady arterial load and arterial wave reflections. Bottom row: measures of pulsatile arterial load. P-value for the ANOVA is indicated in each graphic. In addition, the brackets and * represent a significant pairwise comparison with P≤0.05.

AI_x: augmentation index. cfPWV: carotid-femoral pulse wave velocity. cDBP: central diastolic blood pressure. cSBP: central systolic blood pressure. Central PP: central pulse pressure. GRC: global reflection coefficient. PAC: proximal aortic compliance. P_b: reflected pressure wave amplitude. PE: preeclampsia. P_f: forward pressure wave amplitude. SVR: systemic vascular resistance. TAC: total arterial compliance. Z_c: aortic characteristic impedance.

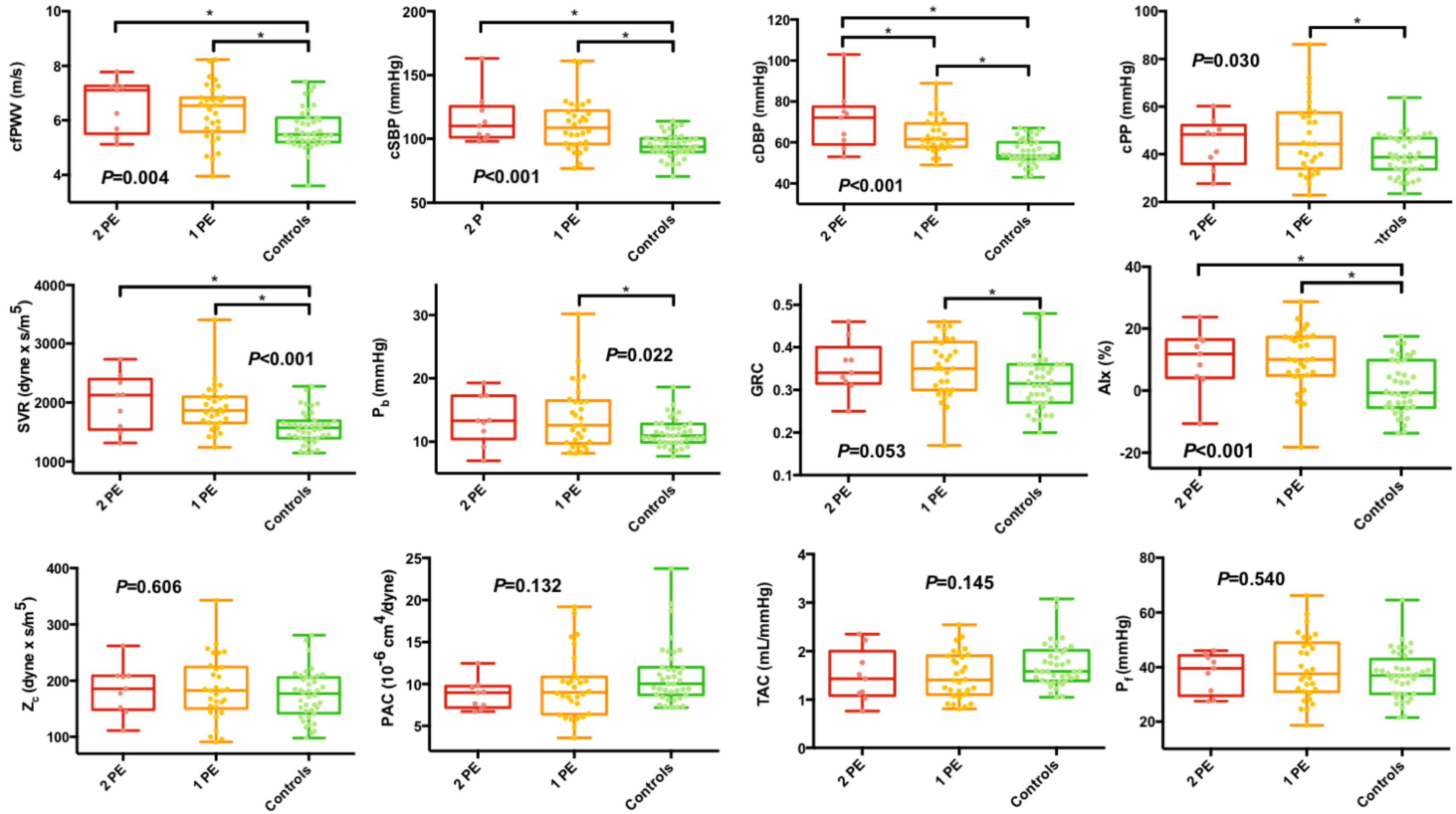
Figure S2. Unadjusted comparisons of arterial hemodynamics among women with preterm preeclampsia, term preeclampsia, and controls with previous normotensive pregnancies.



Top row: measures of aortic stiffness and central blood pressure. Middle row: measures of steady arterial load and arterial wave reflections. Bottom row: measures of pulsatile arterial load. P-value for the ANOVA is indicated in each graphic. In addition, the brackets and * represent a significant pairwise comparison with P≤0.05.

AI_x: augmentation index. cfPWV: carotid-femoral pulse wave velocity. cDBP: central diastolic blood pressure. cSBP: central systolic blood pressure. Central PP: central pulse pressure. GRC: global reflection coefficient. PAC: proximal aortic compliance. P_b: reflected pressure wave amplitude. PE: preeclampsia. P_f: forward pressure wave amplitude. SVR: systemic vascular resistance. TAC: total arterial compliance. Z_c: aortic characteristic impedance.

Figure S3. Unadjusted comparisons of arterial hemodynamics among women with preeclampsia, recurrent preeclampsia, and controls with previous normotensive pregnancies.



Top row: measures of aortic stiffness and central blood pressure. Middle row: measures of steady arterial load and arterial wave reflections. Bottom row: measures of pulsatile arterial load. P-value for the ANOVA is indicated in each graphic. In addition, the brackets and * represent a significant pairwise comparison with $P \leq 0.05$.

AIx: augmentation index. cfPWV: carotid-femoral pulse wave velocity. cDBP: central diastolic blood pressure. cSBP: central systolic blood pressure. Central PP: central pulse pressure. GRC: global reflection coefficient. PAC: proximal aortic compliance. Pb: reflected pressure wave amplitude. PE: preeclampsia. Pf: forward pressure wave amplitude. SVR: systemic vascular resistance. TAC: total arterial compliance. Zc: aortic characteristic impedance.