Maternal hemodynamics: a method to classify hypertensive disorders of pregnancy

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BACKGROUND: The classification of hypertensive disorders of pregnancy is based on the time at the onset of hypertension, proteinuria, and other associated complications. Maternal hemodynamic interrogation in hypertensive disorders of pregnancy considers not only the peripheral blood pressure but also the entire cardiovascular system, and it might help to classify the different clinical phenotypes of this syndrome.

OBJECTIVE: This study aimed to examine cardiovascular parameters in a cohort of patients affected by hypertensive disorders of pregnancy according to the clinical phenotypes that prioritize fetoplacental characteristics and not the time at onset of hypertensive disorders of pregnancy.

STUDY DESIGN: At the fetal-maternal medicine unit of Ziekenhuis Oost-Limburg (Genk, Belgium), maternal cardiovascular parameters were obtained through impedance cardiography using a noninvasive continuous cardiac output monitor with the patients placed in a standing position. The patients were classified as pregnant women with hypertensive disorders of pregnancy who delivered appropriate- and small-for-gestational-age fetuses. Normotensive pregnant women with an appropriate-for-gestational-age fetus at delivery were enrolled as the control group. The possible impact of obesity (body mass index $\geq$30 kg/m^2) on maternal hemodynamics was reassessed in the same groups.

RESULTS: Maternal age, parity, body mass index, and blood pressure were not significantly different between the hypertensive disorders of pregnancy/appropriate-for-gestational-age and hypertensive disorders of pregnancy/small-for-gestational-age groups. The mean uterine artery pulsatility index was significantly higher in the hypertensive disorders of pregnancy/small-for-gestational-age group. The cardiac output and cardiac index were significantly lower in the hypertensive disorders of pregnancy/small-for-gestational-age group (cardiac output 6.5 L/min, cardiac index 3.6) than in the hypertensive disorders of pregnancy/appropriate-for-gestational-age group (cardiac output 7.6 L/min, cardiac index 3.9) but not between the hypertensive disorders of pregnancy/appropriate-for-gestational-age and control groups (cardiac output 7.6 L/min, cardiac index 4.0). Total vascular resistance was significantly higher in the hypertensive disorders of pregnancy/small-for-gestational-age group than in the hypertensive disorders of pregnancy/appropriate-for-gestational-age group and the control group. All women with hypertensive disorders of pregnancy showed signs of central arterial dysfunction. The cardiovascular parameters were not influenced by gestational age at the onset of hypertensive disorders of pregnancy, and no difference was observed between the women with appropriate-for-gestational-age fetuses affected by preeclampsia or by gestational hypertension with appropriate-for-gestational-age fetuses. Women in the obese/hypertensive disorders of pregnancy/appropriate-for-gestational-age and obese/hypertensive disorders of pregnancy/small-for-gestational-age groups showed a significant increase in cardiac output, as well as significant changes in other parameters, compared with the nonobese/hypertensive disorders of pregnancy/appropriate-for-gestational-age and nonobese/hypertensive disorders of pregnancy/small-for-gestational-age groups.

CONCLUSION: Significantly low cardiac output and high total vascular resistance characterized the women with hypertensive disorders of pregnancy associated with small for gestational age due to placental insufficiency, independent of the gestational age at the onset of hypertension. The cardiovascular parameters were not significantly different in the women with appropriate-for-gestational-age or small-for-gestational-age fetuses affected by preeclampsia or gestational hypertension. These findings support the view that maternal hemodynamics may be a candidate diagnostic tool to identify hypertensive disorders in pregnancies associated with small-for-gestational-age fetuses. This additional tool matches other reported evidence provided by uterine Doppler velocimetry, low vascular growth factors in the first trimester, and placental pathology. Obesity is associated with a significantly higher cardiac output and outweighs other determinants of hemodynamics in pregnancy; therefore, in future studies on hypertensive disorders, obesity should be studied as an additional disease and not simply as a demographic characteristic.

Key words: appropriate for gestational age, body mass index, cardiac output, cardiovascular hemodynamics, eclampsia, hypertensive disorders of pregnancy, obesity, preeclampsia, small for gestational age, total vascular resistance

Introduction

Maternal blood pressure (BP) has been used as a robust tool for diagnosing, classifying, and therapeutic targeting of hypertensive disorders of pregnancy (HDP).[1]

Among HDP, preeclampsia (PE) represents a huge burden to obstetrical and neonatal outcome and long-term outcome of women with PE in pregnancy: there are recent studies about short-term cost of PE,[2] the health economic burden of PE,[3] and evidence that PE increases cardiovascular risk in the fifth decade of life.[4] Moreover, recent studies have uncovered that early treatment of critical BP decreased the risk of eclampsia and severe maternal morbidity,[5] and that the history of PE is associated with a risk of coronary artery calcification 3 decades later.[6] In addition to these important impacts of PE, a large retrospective

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cohort study[7] conducted in 15 hospitals participating in the California Maternal Quality Care Collaborative on women with severe intrapartum hypertension (systolic BP >160 mm Hg or diastolic BP >105 mm Hg) proved that these women also had a significantly higher risk of severe maternal morbidity compared to women without severe hypertension.

In all these studies BP had been the key classification criteria. Indeed, BP, although easy to measure in all clinical settings, is the result of cardiac output and total vascular resistance (TVR). TVR is the result of many physiologic factors, including endothelial function, as well as the target of maternal inflammatory response to placental and metabolic dysfunction.[8]

In pregnancy, different placental conditions might damage the maternal endothelium, making this dysfunction the common gateway for HDP. In 1996, Ness and Roberts[9] suggested that altered endothelial cell dysfunction is the common result of circulating factors either resulting from early reduced placental perfusion or from "maternal disorders preexisting… pregnancy." In 2006, with similar but updated interpretations, Borzychowski et al[10] proposed that PE can develop in the presence of a normal size placenta in women affected by systemic inflammation. The placental pathology that supports this interpretation of PE has been more recently reviewed by Redman et al[11] and Staff et al,[12] who showed how oxidative stressed syncytiotrophoblast oversecretes proteins that contribute to the pathogenesis of hypertension and organ lesions through endothelial damage. However, early-onset PE has an extrinsic cause (ie, poor placentation), whereas late-onset PE has an intrinsic cause—microvillous overcrowding—as placental growth reaches its functional limit.[11]

The implications of these studies could be supported by the interrogation of maternal cardiovascular hemodynamics in HDP. In fact, in the last decade, many studies observed that maternal cardiac output is reduced in the typical clinical phenotype of early-onset PE, which is more frequently associated with poor placentation and fetal growth restriction, whereas maternal cardiac output appears to be increased in the typical phenotype of late-onset PE,[13-15] which is more frequently associated with preexisting cardiovascular risk factors.[10,11,14]

Consequently, we hypothesized that cardiovascular dysfunctional adaptation to pregnancy could be a more powerful diagnostic tool than the time at the onset of high BP to understand the different conditions associated with the primary placental phenotypes that characterize HDP.

This study aimed to examine the maternal hemodynamics of a prospective cohort according to the clinical phenotypes that prioritize fetoplacental characteristics, and maternal obesity as a proxy of metabolic syndrome, rather than the time at onset of HDP.

Materials and Methods

We analyzed the original database of a cohort of women with gestational hypertension (GH) or PE reported in 2015[16] according to the classification of the Working Group on High Blood Pressure in Pregnancy. Additional prospective data were gathered (to date), including demographic, clinical, and unpublished data, such as uterine artery Doppler velocimetry and body surface area (BSA), by retrieving original measurements from clinical records forms.[17] In addition, we calculated TVR using an established formula.[13]

All cases were recruited at the fetal-maternal medicine unit of Ziekenhuis Oost-Limburg (Genk, Belgium). In this cohort, women with singleton pregnancies who were admitted for new-onset hypertension week >20 were considered for inclusion, and enrolled by informed signed consent. Approval of the ethical committee was obtained before study onset (MEC ZOL reference: 08/049, 09/050, and 10/065).

HDP were defined according to the criteria of the National High Blood Pressure Education Program Working Group[1]; for the purposes of this study, chronic hypertension, with or without superimposed PE, was excluded. Women with any maternal disease or who later developed HELLP syndrome were excluded from this study.

Using a noninvasive continuous cardiac output monitor (NICCOMO, Software Version 2.0; Medis Medizinische Messtechnik GmbH, Ilmenau, Germany), cardiovascular parameters were obtained through impedance cardiography with the women in a standing position, according to a previously reported, repeatable method.[18-20] The impedance cardiography parameters were the left ventricular output and aortic flow parameters. The left ventricular output parameters were the stroke volume (SV) (in mL), heart rate (HR) in beats/min, and cardiac output in L/min (cardiac output = HR × SV). The aortic flow parameters were the aortic velocity index (VI) (expressed in 1/1000/s), which is equivalent to the amplitude of the systolic wave, and the aortic acceleration index (ACI) (expressed in 1/100/s), which represents the maximum acceleration of blood flow in the aorta.[21]

In this larger, updated prospective cohort, we identified 2 homogenous groups of pregnant women affected by HDP, as defined above, classified according to the newborn weight centile (above or below the 10th centile), according to local standards[22] to select the following 2 groups: (1) the HDP/appropriate-for-gestational-age (AGA) group; and (2) the HDP/small-for-gestational-age (SGA) group. The demographic, clinical, and hemodynamic findings of these 2 groups were then compared to a control group of women with uneventful pregnancies.

The first step of this study was the analysis and comparison of the cardiovascular indices observed in these 2 groups affected by HDP according to their association with AGA or SGA newborns. Cardiac output was also analyzed after it was normalized for the BSA[17] because the cardiac index is supposed to correct the cardiac output for the real volume of distribution of blood flow.

The second step of this analysis was performed to compare these 2 groups,

TABLE 1
Maternal characteristics, laboratory results, and neonatal characteristics of hypertensive disorders of pregnancy/appropriate for gestational age, hypertensive disorders of pregnancy/small-for-gestational-age, and control groups

	Group			*P* values for between-group comparisons		
Variable	Control	HDP-AGA	HDP-SGA	HDP-AGA vs control	HDP-SGA vs control	HDP-AGA vs HDP-SGA
N	33	142	41			
Maternal age, y	30 (27–33)	29 (26–32)	29 (27–32)	.5	.4	.9
BMI, kg/m^2	23.3 (19.8–28.4)	24.9 (22.7–28.7)	24.0 (21.5–29.3)	.2	.9	.2
Nulliparous	15 (45%)	36 (25%)	12 (29%)	.03	.2	.7
GA at examination	34^{+5} (32^{+1}–39^{+0})	37^{+3} (36^{+3}–38^{+4})[a]	36^{+0} (32^{+6}–37^{+6})	.06	1.0[a]	.01[a]
Hemoglobin, g%	12.5 (11.4–12.8)	12.0 (11.3–12.9)	12.9 (12.2–13.9)	.3	.04[a]	.0006[a]
Thrombocyte count, $\times$1000/mm^3	197 (156–240)	190 (158–225)	189 (160–223)	1.0	.7[a]	.8[a]
Uric acid, μmol/L	4.52 (3.63–5.66)[a]	5.68 (4.84–6.58)[a]	6.34 (5.58–7.14)[a]	.0000[a]	.0000[a]	.002[a]
24-h urine protein, mg	153 (117–179)[a]	359 (187–925)[a]	672 (334–2495)[a]	.0000[a]	.0000[a]	.013[a]
Mean uterine artery PI	0.66 (0.53–0.83)	0.69 (0.57–0.87)	0.93 (0.71–1.16)[a]	.4	.001[a]	.0001[a]
GA at birth, wk	39^{+1} (36^{+4}–40^{+1})	38^{+1} (36^{+2}–39^{+3})	36^{+0} (33^{+4}–38^{+2})[a]	.1	.003[a]	.002[a]
Birthweight, g	3235 (2590–3545)	2992 (2645–3470)	2015 (1477–2450)[a]	.4	.0000[a]	.0000[a]
Male gender	20 (62.5%)	66 (46.5%)	23 (56.1%)	.1	.6	.3
Birthweight percentile	47.5 (22.5–65)	45 (25–70)	5 (2.5–7.5)[a]	.7	.0000[a]	.0000[a]

Data are reported as median (interquartile range) or n (%) unless otherwise specified.

AGA, appropriate for gestational age; *BMI*, body mass index; *GA*, gestational age; *HDP*, hypertensive disorders of pregnancy; *PI*, pulsatility index; *SGA*, small for gestational age.

[a] *P* values significant at level of $\alpha = 0.05$, after applying Bonferroni correction for multiple comparisons $\alpha = 0.02$.

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including the same cardiac indices observed in the early and late third trimester, <34 and >34 weeks of gestation, to determine whether the step-1 results were biased by gestational age at the time of examination in the affected groups and the controls.

The third analytical step was performed to compare the maternal hemodynamic in patients affected by GH or by PE delivered of AGA newborns to analyze whether proteinuria had any influence on maternal hemodynamics.

The fourth analysis was performed on the 2 HDP-AGA and HDP-SGA groups to compare the subgroups of women with a body mass index (BMI) >30 or <30 at the time of examination. This analysis was performed to estimate the possible impact of obesity on maternal hemodynamics in pregnant patients affected by HDP.

The final analysis was made on the entire cohort, which was then traditionally classified as early-onset PE, late-onset PE, and GH.[1]

The cardiovascular indices observed in these 2 groups and in the control group selected for this post hoc analysis were statistically compared. We used the Mann-Whitney rank-sum nonparametric test or 2-tailed *t* tests, as appropriate, to compare continuous variables between pairs of groups. Fisher exact 2-tailed test was used to determine the significance of association in 2 × 2 contingency tables. For statistical comparisons, the level of significance was set at $\alpha = 0.05$. When >2 groups were simultaneously compared, the Bonferroni method was also used to assess more stringent *P* values by dividing .05 by the number of comparisons. Unless specified, all data are reported as the median (interquartile range [IQR]) or the number (percentage) of women. All statistical analyses were performed using software (Stata/IC 14.1; StataCorp LP, College Station, TX).

Results

The present updated cohort analyzed 216 cases under this different tentative stratification of cases.

Table 1 summarizes the maternal characteristics, laboratory results, and neonatal outcomes of the control, HDP-AGA, and HDP-intrauterine growth restriction (IUGR) groups. The 3 groups were similar in terms of the maternal age, BMI, and hemoglobin concentration. Note that maternal age, BMI, and parity were not significantly different between the groups.

Table 2 presents the cardiovascular parameters for the control, HDP-AGA, and HDP-IUGR groups. BP was not significantly different between the

TABLE 2
Comparison of cardiovascular parameters in hypertensive disorders of pregnancy/appropriate for gestational age, hypertensive disorders of pregnancy/small-for-gestational-age, and control groups

Variable	Group			*P* values for between-group comparisons		
	Control	HDP-AGA	HDP-SGA	HDP-AGA vs control	HDP-SGA vs control	HDP-AGA vs HDP-SGA
N	33	142	41			
MAP, mm Hg	95.5 (88–107)[a]	112 (104–118)	110 (103–117)	.0000[a]	.0000[a]	.6
Heart rate, beats/min	99 (91–108)	93 (87–105)	93 (82–101)	.4	.09	.1
Stroke volume, mL	78 (68–88)	81.5 (65–95)	75 (60–90)	.8	.3	.1
Cardiac output, L/min	7.6 (7.0–8.4)	7.6 (6.2–8.9)	6.5 (6.0–7.7)[a]	.8	.007[a]	.006[a]
Cardiac index	4.0 (3.8–4.4)	3.9 (3.4–4.5)	3.6 (3.3–4.0)[a]	.1	.0004[a]	.02[a]
TVR, dynes/s/cm^{-5}	1082 (905–1175)[a]	1214 (1020–1451)[a]	1399 (1198–1563)[a]	.002[a]	.0000[a]	.008[a]
VI, 1/1000/s	61 (54–76)[a]	46 (39–56)	49 (40–58)	.0000[a]	.0002[a]	.5
ACI, 1/100/s^2	118 (93–147)[a]	86 (72–116)	84 (67–124)	.0001[a]	.003[a]	.9

Data are reported as median (interquartile range) unless otherwise specified.

ACI, acceleration index; *AGA*, appropriate for gestational age; *HDP*, hypertensive disorders of pregnancy; *MAP*, mean arterial pressure; *SGA*, small for gestational age; *TVR*, total vascular resistance; *VI*, velocity index.

[a] *P* values significant at level of $\alpha = 0.05$, after applying Bonferroni correction for multiple comparisons, $\alpha = 0.02$.

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HDP groups. Cardiac output was significantly lower in the HDP-IUGR group than in the HDP-AGA group. TVR was significantly greater in the HDP-IUGR group than in HDP-AGA and control groups.

The BSA in the entire cohort of HDP-AGA women (1.99 ± 0.22 m^2) was significantly greater ($P < .03$) than that in the entire cohort (nonobese and obese) of HDP-SGA women (1.90 ± 0.16 m^2) and control women (1.89 ± 0.16 m^2). Note that the cardiac index (cardiac output corrected for BSA) in the entire cohort of HDP-AGA women was not significantly different from that in the control group; however, it remained significantly greater than that observed in the HDP-SGA women.

Compared with the women with normal pregnancies, all women with HDP showed signs of central arterial hemodynamic dysfunction, as illustrated by their low aortic VI and ACI values.

Table 3 shows the cardiovascular parameters in the 2 groups according to early and late onset of the hypertensive disorder in HDP patients with AGA and SGA fetuses. None of the cardiovascular parameters were influenced by gestational age at onset in the third trimester.

A subgroup analysis was conducted for patients with AGA fetuses with PE or of GH. Maternal age, BMI, uterine artery pulsatility index, and normal birthweight centile were not significantly different. The median gestational age at the cardiographic examination differed by only 1 week, albeit proving a significant difference for a skewed distribution of weeks at delivery in patients with PE (29 weeks, IQR 26-32; vs 30 weeks, IQR 26-33) (Supplemental Table). Table 4 shows the cardiovascular parameters of this subgroup analysis. With the exception of HR, none of the cardiovascular parameters proved to be significantly higher (5 beats/min on average) in women with GH.

A similar subanalysis was performed for the patients who had SGA fetuses and PE (33 patients) or GH (8 patients). The small number of the latter cases did not allow us to perform a meaningful statistical assessment. The cardiac output and cardiac index of PE-SGA patients were 6.5 L/min (IQR 6.0-7.1) and 3.6 (IQR 3.1-3.9), respectively. TVR was 1400 dynes/s/cm^{-5} (IQR 1232-1569); VI and ACI were 48 1/1000/s (IQR 38-58), and 84 (IQR 66-121). The median values of this subgroup closely matched the median values of the entire cohort of HDP-SGA patients, albeit with a different, smaller variance.

Table 5 shows the highly significant impact that obesity had on cardiovascular parameters, primarily on patients with HDP-SGA.

Table 6 shows the cardiovascular parameters of the entire cohort classified using the same criteria[1] adopted from the first reported study.[16]

Comment

Principal findings

The cardiovascular parameters observed in the entire cohort classified according to the same criteria as previously reported on a smaller cohort[16] confirmed that none of these parameters were significantly different among early-onset PE, late-onset PE, and GH. SV, cardiac output, and cardiac index were not significantly different in patients affected by early and late PE and GH compared with those of the control group. In fact, the classification of the National High Blood Pressure Education Program Working Group[1] by definition does not take into account maternal cardiovascular parameters.

TABLE 3
Comparison of cardiovascular parameters between hypertensive disorders of pregnancy groups, appropriate vs small for gestational age; <34 and >34 weeks of gestation

	HDP-AGA ≤34 wk	HDP-AGA >34 wk	*P*	HDP-SGA ≤34 wk	HDP-SGA >34 wk	*P*[a]
No. of patients	25	117		16	25	
SBP, mm Hg	149 (139–164)	149 (139–160)	.9	144 (132–154)	149 (138–157)	.3
DBP, mm Hg	101 (93–102)	98 (94–105)	.8	97 (92–105)	99 (95–100)	.6
MAP, mm Hg	111 (105–118)	112 (104–118)	1.0	110 (102–117)	110 (107–115)	.6
Heart rate, beats/min	98 (85–106)	93 (87–105)	1.0	93 (83–99)	93 (82–101)	.7
Stroke volume, mL	74 (63–83)	83 (67–97)	.2	76 (65–96)	74 (59–86)	.4
Cardiac output, L/min	7.3 (6.0–8.9)	7.6 (6.3–8.9)	.4	6.7 (6.0–7.7)	6.4 (6.0–7.7)	.5
Cardiac index	3.9 (3.4–4.4)	3.8 (3.3–4.6)	.5	3.7 (3.2–4.1)	3.5 (3.3–3.9)	.6
TVR, dynes/s/cm^{-5}	1220 (1005–1678)	1214 (1026–1451)	.9	1329 (1156–1608)	1400 (1223–1527)	.6
VI, 1/1000/s	45 (37–58)	46 (39–56)	.8	45 (36–58)	49 (41–61)	.5
ACI (1/1000/S^2)	83 (63–113)	86 (73–116)	.5	77 (65–122)	86 (71–128)	.4

Data are reported as median (interquartile range) unless otherwise specified.

ACI, acceleration index; *AGA*, appropriate for gestational age; *DBP*, diastolic blood pressure; *HDP*, hypertensive disorders of pregnancy; *MAP*, mean arterial pressure; *SBP*, systolic blood pressure; *SGA*, small for gestational age; *TVR*, total vascular resistance; *VI*, velocity index.

[a] *P* values were significant at level of $\alpha = 0.05$, after applying Bonferroni correction for multiple comparisons, $\alpha = 0.02$.

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When the entire cohort of patients affected by HDP was grouped by prioritizing fetal growth, we observed that the patients with hypertensive disorders (according to the definition used in our study, only those with PE or GH) and SGA fetuses (HDP-SGA) had highly significantly lower cardiac output than those patients with hypertensive disorders and normal fetuses (HDP-AGA). Such a high cardiac output difference between groups was robust enough that the cardiac index (cardiac output corrected for the body surface) remained significantly lower in the HDP-SGA group, even if BSA was significantly lower in the HDP-IUGR group than in the HDP-AGA and control groups. Similarly, highly significant higher TVR was observed in patients affected by HDP-SGA than in patients with HDP-AGA. Increased TVR was paralleled by significantly lower values of VI and ACI, which represented the amplitude of the systolic wave and the maximum acceleration of blood flow in the aorta, respectively, as they are computed by the noninvasive continuous cardiac output monitor (NICCOMO). However, in HDP-SGA patients, these lower values observed in the aorta were accompanied by a low cardiac output and high TVR, which together determined a worse placental perfusion.

These highly significant differences in maternal cardiovascular parameters

TABLE 4
Comparison of cardiovascular parameters between preeclampsia and gestational hypertension appropriate-for-gestational-age groups

	PE-AGA	GH-AGA	*P*
N	90	52	
SBP, mm Hg	149 (139–164)	149 (137–160)	.8
DBP, mm Hg	98 (94–103)	99 (93–105)	.9
MAP, mm Hg	112 (105–118)	112 (104–118)	.8
Heart rate, beats/min	91 (84–104)	96 (89–110)	.04[a]
Stroke volume, mL	82 (67–93)	80 (62–97)	.8
Cardiac output, mL/min	7.6 (6.2–8.9)	7.6 (6.2–9.1)	.7
Cardiac index	3.9 (3.4–4.4)	3.9 (3.3–4.5)	.8
TVR, dynes/s/cm^{-5}	1220 (1038–1487)	1158 (983–1440)	.6
VI, 1/1000/s	47 (39–56)	46 (39–57)	.9
ACI	86 (73–118)	84 (66–116)	.8

Data are reported as median (interquartile range) unless otherwise specified.

For maternal demographics and clinical data, see Supplemental Table.

ACI, acceleration index; *AGA*, appropriate for gestational age; *DBP*, diastolic blood pressure; *GH*, gestational hypertension; *MAP*, mean arterial pressure; *PE*, preeclampsia; *SBP*, systolic blood pressure; *TVR*, total vascular resistance; *VI*, velocity index.

[a] *P* values significant at level of $\alpha = 0.05$, after applying Bonferroni correction for multiple comparisons, $\alpha = 0.02$. [a] is reported for each group that proved to be significantly different.

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TABLE 5
Comparison of cardiovascular parameters between nonobese (body mass index <30) and obese (body mass index ≥30) women divided by hypertensive disorders of pregnancy, appropriate vs small for gestational age

	Nonobese HDP-AGA	Obese HDP-AGA	*P*	Nonobese HDP-SGA	Obese HDP-SGA	*P*
No. of patients	112	25		32	9	
BMI, kg/m^2	24.1 (22.1–27.1)[a]	33.5 (31.7–37.3)[a]	.0001[a]	23.4 (21.9–25.6)	31.2 (31.1–33.9)[a]	.0001[a]
MAP, mm Hg	111 (104–118)	116 (107–125)	.1	111 (104–115)	110 (103–122)	.5
Heart rate, beats/min	92 (87–104)	104 (84–111)	.09	93 (82–100)	94 (86–103)	.4
Stroke volume, mL	81 (63–92)	83 (71–105)	.2	70 (58–80)[a]	93 (88–99)[a]	.004[a]
Cardiac output, L/min	7.4 (6.1–8.7)[a]	8.3 (7.4–10.6)[a]	.009[a]	6.3 (5.8–7.0)[a]	8.7 (8.3–9.1)[a]	.0004[a]
Cardiac index	3.9 (3.4–4.4)	3.9 (3.3–4.6)	.8	3.5 (3.1–3.7)[a]	4.2 (3.9–4.3)[a]	.005[a]
TVR, dynes/s/cm^{-5}	1223 (1036–1487)	1137 (917–1403)	.1	1451 (1289–1622)[a]	1152 (1026–1248)[a]	.0005[a]
VI, 1/1000/s	49 (40–58)[a]	38 (30–41)[a]	.0001[a]	50 (41–63)	44 (38–49)	.1
ACI	93 (77–127)[a]	72 (53–80)[a]	.0001[a]	100 (69–129)[a]	71 (53–80)[a]	.04[a]

Data are reported as median (interquartile range) unless otherwise specified.

ACI, acceleration index; *AGA*, appropriate for gestational age; *BMI*, body mass index; *HDP*, hypertensive disorders of pregnancy; *MAP*, mean arterial pressure; *SGA*, small for gestational age; *TVR*, total vascular resistance; *VI*, velocity index.

[a] *P* values significant at level of $\alpha = 0.05$, after applying Bonferroni correction for multiple comparisons, $\alpha = 0.02$.

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were not determined by the occurrence of hypertensive disorders <34 or >34 weeks of gestation nor by the presence or absence of PE with AGA fetuses or SGA fetuses.

As expected, obesity played a significant role, both in HDP-AGA and HDP-SGA, in changing maternal cardiovascular parameters into high cardiac output normal peripheral resistance, with an even lower amplitude of the systolic wave and maximum acceleration of blood flow. In fact, obesity is a disease per se, and because of its impact on metabolism and the autonomic nervous and cardiovascular systems, it should be treated as such in biological studies and possibly in clinical cohorts.

Interpretation of the findings in HDP with SGA

In the present analysis, in which we hypothesized a possible association between placental insufficiency with fetal growth restriction and maternal cardiovascular dysfunction in HDP, we observed marked differences in all cardiovascular parameters between the HDP-AGA and HDP-SGA groups. Such important differences would have been lost if PE had been classified according to gestational age at onset without considering a possible role of maternal hemodynamics in the cross-talk between the developing placenta and maternal cardiovascular condition.[23]

An association between birthweight and vascular resistance was first reported in 1991 by Easterling et al.[24] A direct relationship between birthweight and maternal cardiac output had been more recently reported in women with IUGR[25] and PE.[26] Moreover, abnormal central arterial hemodynamics[27] and suboptimal plasma volume expansion with low aldosterone serum concentrations[28] have been reported in women with PE associated with poor fetal growth.

Our findings align with the interpretation of data reported in an early study by Valensise et al.[13] In fact, they observed that as early as 24 weeks of gestation, cardiac output was lower and TVR was higher in women who later developed early PE than in women who developed late PE. In that reported cohort with early-onset PE, 60% of the uterine artery Doppler velocimetric values were abnormal vs 17% in late-onset PE, and the birthweight percentile was 18 ± 12 vs 48 ± 20 in late-onset PE. The BMI was 23 kg/m^2 in early-onset PE vs 28 kg/m^2 in late-onset PE. As we can see from the weight centile at birth, uterine Doppler and maternal BMI, the temporal classification adopted by that study, mixed different phenotypes in terms of feto-placental growth and maternal risk of metabolic syndrome. Unfortunately, when the temporal classification is adopted, one misses the chance to investigate among late-onset PE cases the possible different cardiovascular adaptation of cases in which PE was associated with IUGR.

Other important studies have investigated the complex cardiac dysfunction and altered myocardial remodeling that affects 40% of women who develop PE at term,[29] and one third of women who develop PE, regardless of gestation, demonstrated similar evidence of left ventricular hypertrophic concentric remodeling. However, only women with preterm PE appear to develop a high-resistance/low-volume hemodynamic state at midgestation.[15] Again, the study by Melchiorre et al,[15] as well as the study by Valensise et al[13] discussed above, studied 18 cases of early-onset PE in

TABLE 6
Cardiovascular parameters of entire cohort classified according to early- and late-onset preeclampsia and gestational hypertension

	Control	Early PE	Late PE	GH	*P*
N	33	39	84	60	
SBP, mm Hg	132 (119–144)[a]	149 (135–158)[b]	149 (138–163)[b]	149 (137–160)[b]	.0000[a]
DBP, mm Hg	85 (78–95)[a]	100 (92–104)[b]	98 (94–104)[b]	98 (92–105)[b]	.0000[a]
MAP, mm Hg	96 (87–107)[a]	111 (103–117)[b]	112 (105–119)[b]	111 (104–118)[b]	.0000[a]
Heart rate, beats/min	99 (88–108)[a]	93 (85–104)	90 (84–103)[b]	96 (89–111)	.02[a]
Stroke volume, mL	78 (68–89)	75 (63–88)	82 (65–94)	81 (61–96)	.8
Cardiac output, L/min	7.6 (6.9–8.4)	6.9 (6.0–8.9)	7.2 (6.1–8.5)	7.6 (6.1–8.9)	.4
Cardiac index	4.0 (3.7–4.5)	3.7 (3.3–4.4)	3.8 (3.4–4.3)	3.9 (3.4–4.5)	.08
TVR, dynes/s/cm^{-5}	1082 (898–1176)[a]	1276 (1043–1621)[b]	1246 (1062–1501)[b]	1158 (1011–1436)[b]	.0009[a]
VI, 1/1000/s	61 (54–76)[a]	45 (36–58)[b]	48 (39–57)[b]	47 (39–58)[b]	.0000[a]
ACI, 1/100/s^2	118 (91–149)[a]	80 (64–119)[b]	88 (73–121)[b]	84 (70–126)[b]	.0009[a]

Data are reported as median (interquartile range) unless otherwise specified.

Analysis adjusted for multiple comparisons. Kruskal-Wallis test was adopted.

ACI, acceleration index; *DBP*, diastolic blood pressure; *GH*, gestational hypertension; *MAP*, mean arterial pressure; *PE*, preeclampsia; *SBP*, systolic blood pressure; *TVR*, total vascular resistance; *VI*, velocity index.

[a] *P* values significant at level of $\alpha = 0.05$, after applying Bonferroni correction for multiple comparisons, $\alpha = 0.02$; [b] Significant difference compared to control group.

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women who delivered babies with a median birthweight percentile of 4.7 (IQR 2-7).

Thanks to this background information, it is not difficult to agree that "it is certainly plausible that the placenta causes PE and IUGR in the minority of cases."[23] However, it is difficult to imagine that fetoplacental growth restriction stops its decisive cross-talk with the maternal cardiovascular system at 34 weeks of gestation and ceases its role. By definition, the present classification, which is based on onset of hypertension and proteinuria, does not consider either the different placental pathologies that cause a similar oxidative stress of the syncytiotrophoblast early in gestation due to shallow trophoblastic invasion (as indicated by low placental growth factor and high uterine Doppler pulsatility index[24] and fetal growth restriction), and later in gestation due to villi overcrowding,[11,30] nor the possible different maternal cardiovascular performance that we observed in this study by a simplistic but effective association of hypertensive disorders with a robust classification of normal or restricted fetal growth.

Interpretation of the findings in HDP and obesity

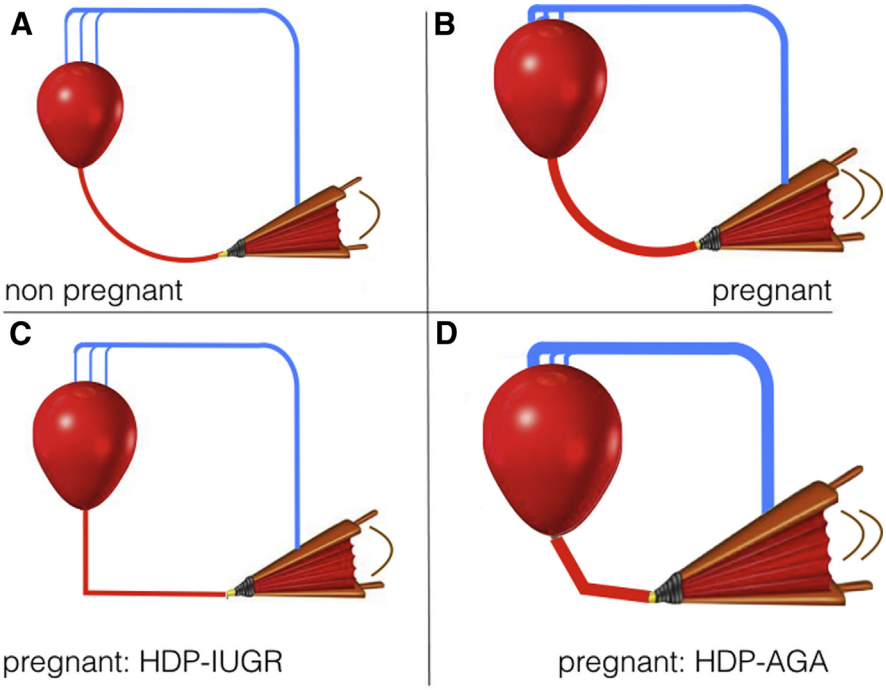
Nonpregnant obese individuals typically have high cardiac output, mainly due to a large circulating volume[31] and a low TVR, which results from a shift of noncirculating stored splanchnic venous blood into the circulation by increased central sympathetic activity[32] and from increased aldosterone activity.[33] The latter condition might depend on visceral obesity-related compression of the kidneys[32] or the release of leptin, an aldosterone agonist, from adipocytes.[34]

In this study, despite its low prevalence, we tried to analyze the impact of maternal obesity on cardiovascular function in pregnant women with HDP. We found that cardiac output increased by approximately 0.9 L/min both in women with HDP-AGA and 2.4 L/min in women with HDP-SGA. The average BMI difference in the 2 groups was 9.4 and 7.8 kg/m^2, respectively. The observed increase in cardiac output was much more than 0.1 L/min per 1 kg/m^2 (1 BMI U), as expected as a simple direct effect of increasing BMI.[35] These findings challenge the mechanistic correction of cardiac output for BSA in obese pregnant women. Despite the tremendous difference in tissue perfusion between adipose tissue and the fetoplacental unit, some authors do correct cardiac output for BSA[15,29] and calculate the cardiac index. Based on the above reported findings,[35] we calculated that 5 kg of fat mass receives 250 mL/min of blood at rest and possibly less in obese pregnant women with dysfunctional leaking endothelium, whereas a 5 kg fetoplacental unit, including the amniotic fluid, receives between 450[27,36]-830 mL/min.[37,38] Until adequate hemodynamic models are implemented, the cardiac output value represents the cardiac strain and adaptation better than indices derived from nonpregnant women.

Clinical implications

Pregnancies associated with HDP differ from normal pregnancies in terms of abnormal cardiovascular hemodynamics. Our findings suggest that women with HDP and SGA fetuses and those with HDP and AGA fetuses have different hemodynamic dysfunctions

FIGURE
Simplified schematic presentation of type-specific hemodynamics



A, nonpregnant state; **B**, normal pregnancy; **C**, hypertensive disorders of pregnancy (HDP) and intrauterine growth restriction (IUGR); and **D**, HDP-appropriate for gestational age (AGA) or even large for gestational age. In nonpregnant state, blood flow to uterine arteries is negligible; at mid-pregnancy, it is 12% of whole cardiac output.[37,38] Dimension of bellow represents dimension of left ventricle beating at given rate, with certain stroke volume (SV) with each blow, at given heart rate (HR), tube diameter, and curvature (smooth = low total vascular resistance [TVR]; steep angle = high TVR) represent TVR; balloon content represents cardiac output (cardiac output = SV × HR). Blood pressure (BP) inside tubes is product of cardiac output and TVR (BP = [f] cardiac output × TVR). Blue vessels are veins and their dimension represents plasma volume relocated in capacitance vessels and in splanchnic venous system. As compared to **A**, nonpregnant state, **B**, normal pregnancy induces increase in SV and cardiac output. These early adaptations are simultaneous with major reduction of TVR that results in lower BP.[47] In parallel, plasma volume increases by 1.2 L at 28 weeks of gestation,[49] with one fourth of it relocated in splanchnic venous system.[21] Suboptimal plasma expansion in pregnancy was observed in pregnancies complicated by preeclampsia and fetal growth restriction.[42] In **C**, HDP-IUGR, SV, HR, and cardiac output are lower than that in **B**, normal pregnancy. TVR is much higher than in both **A** and **B**, resulting in higher BP values[13-15,26] and plasma volume is lower than in normal pregnancies.[38] In **D**, HDP-AGA, reported hemodynamic findings are controversial (see text for discussion). SV and cardiac output are similar or higher, and TVR similar or higher than in **B**, normal pregnancy. In reported cohorts, combination of 2 factors (TVR and cardiac output) results in higher BP. Under physiologic conditions, these fundamentally different states are influenced by many other variables, such as blood viscosity, anatomic and functional vascular wall integrity, and ratio between lean and fat mass.

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(Figure) and should be examined for their cardiovascular performance when maternal or fetal condition require in-hospital monitoring and major antihypertensive treatment. As regards the proper technique to adopt for these examinations, recent studies cover a wide spectrum of noninvasive technologies. We believe that, beyond screening tests, this diagnostic interrogation of maternal cardiovascular system should be performed by cardiologists. PE obviously remains a more serious disease than GH, yet maternal cardiovascular performance should be considered when different antihypertensive drugs are under scrutiny to treat moderate to severe forms of hypertension in pregnancy.[39]

Research implication

Differences in maternal cardiovascular parameter matches other evidences provided by uterine Doppler velocimetry,[5] low vascular growth factors in the first trimester,[24] and placental pathology.[25] Future studies on these predictors and markers of HDP should consider adding maternal cardiovascular parameters in addition to simple peripheral arterial BP. Obesity is associated with higher cardiac output and relatively reduced TVR, as we observed in this study, as well as with significant increase in left ventricular mass as observed by cardiac magnetic resonance imaging.[35] It also significantly outweighs other determinants of hemodynamics in pregnancy and should be studied as an additional disease and not as a simply demographic characteristic.

Both conditions focused on in our study represent a significant risk factor for cardiovascular disease (CVD) later in life. Notably, in the presence of 3 or 4 risk factors for metabolic syndrome, including obesity, the adjusted hazard ratio for CVD later in life might increase by up to 10 times compared to unaffected pregnancies.[40] PE and SGA too are independent risk factors for CVD later in life; the 2 risk factors together, PE with SGA, increase the risk of CVD as much as 8-fold.[41] However, the respective pathophysiologies of these 2 different phenotypes of placental damage and cardiovascular dysfunction appear to be totally different, and it is likely that different preventive and therapeutic strategies should be employed before,[42] during, and after pregnancy, as well as later in life.[43] These problems should be investigated by future longitudinal studies beginning with the early first trimester or even from the preconception phase to the postpregnancy long-term follow-up.

Strengths and limitations

The major limitation of this study is that the only assessment of in utero growth

was the birthweight percentile,[44,45] and we had no data on the longitudinal growth of these fetuses, or early first-trimester molecular[46] or Doppler evidence of poor placentation; however, newborn weight centile allowed us to identify a robust cut-off to prioritize fetal growth instead of gestational age to analyze maternal hemodynamics. Gestational age at the time of examination in the HDP-AGA group was significantly higher than in the HDP-IUGR group; however, the median value between the 2 groups was just 7 days. Such a difference is negligible given the hemodynamic plateau reached early in the third trimester.[47] Our findings on obesity should be considered with caution given the limited number of cases.

The major strength of this study is that the data were analyzed according to a post hoc hypothesis that differed from the temporal classification originally used.[16] This process avoided unwanted subjective bias in terms of collecting and interpreting cardiac function data. In addition, this method allowed us to perform a comparison between 2 models developed using the same methodology for cardiovascular interrogation of women affected by HDP. The results of the first model, published in 2015,[16] were based on the temporal classification of HDP according to the gestational age at onset. The second model, as adopted in this study, was based on a classification that prioritized placental pathology and fetal growth.[11,30,48]

Finally, although correction of cardiac output in pregnancy is controversial, we calculated the BSA for all HDP-AGA, HDP-IUGR, and control groups and corrected the cardiac output by the BSA to determine the cardiac index and allow direct comparisons of our data with previously reported findings. ■

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SUPPLEMENTAL TABLE

Comparison of maternal demographics and clinical data between preeclampsia and gestational hypertension appropriate-for-gestational-age groups

	PE-AGA	GH-AGA	*P*
N	90	52	
Maternal age, y	29 (26–32)	30 (26–33)	.3
BMI, kg/m^2	24.2 (22.6–28.3)	26.9 (23.1–36.6)	.08
GA at examination	37.0 (33.7–38.3)	38.0 (36.9–39.1)	.0009[a]
Hemoglobin, g%	12.0 (11.0–12.7)	12.0 (11.7–13.2)	.2
Thrombocyte count, $\times$1000/mm^3	177 (152–208)	205 (188–244)	.002[a]
Uric acid, μmol/L	5.8 (5.0–6.7)	5.5 (4.7–6.2)	.04[a]
24-h urine protein, mg	756 (373–1473)	169 (131–206)	.0000[a]
Mean uterine artery PI	0.73 (0.60–0.92)	0.62 (0.52–0.84)	.06
GA at birth, wk	37.4 (34.6–38.7)	39.1 (38.3–40.0)	.0000[a]
Birthweight, g	2858 (2179–3271)	3248 (2974–3668)	.0000[a]
Birthweight percentile	40 (25–63)	49 (26–84)	.2

Data are reported as median (interquartile range) unless otherwise specified.

AGA, appropriate for gestational age; *BMI*, body mass index; *GA*, gestational age; *GH*, gestational hypertension; *PE*, preeclampsia; *PI*, pulsatility index.

[a] *P* values significant at level of $\alpha = 0.05$, after applying Bonferroni correction for multiple comparisons, $\alpha = 0.02$.