Maternal hemodynamic profile during pregnancy and in the post-partum in hypertensive disorders of pregnancy and fetal growth restriction

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BACKGROUND: Maternal cardiovascular changes, occurring since the beginning of pregnancy, are necessary for normal placentation and regular evolution of pregnancy.

OBJECTIVE: This study aimed to compare the hemodynamic profiles and cardiac remodeling of women with hypertensive disorders of pregnancy and either appropriate for gestational age fetuses or growth-restricted fetuses, women with normotensive pregnancies complicated by fetal growth restriction, and women with uncomplicated pregnancies, during pregnancy and the postpartum period.

STUDY DESIGN: A prospective longitudinal case–control design was used for this study. Over the study period, 220 eligible women with singleton pregnancies were selected for the analysis and divided into 4 groups: (1) hypertensive disorders of pregnancy with appropriate for gestational age fetuses; (2) hypertensive disorders of pregnancy with fetal growth restriction; (3) normotensive fetal growth restriction; and (4) controls. Ultrasound fetal biometry and fetoplacental Doppler velocimetry were performed at recruitment. Maternal hemodynamic assessment using transthoracic echocardiography was performed at the time of recruitment by a dedicated cardiologist blinded to maternal clinical data. The same assessments were performed in 104 patients at 32 weeks (interquartile range, 24–40) after delivery by the same cardiologist.

RESULTS: During pregnancy, women in the hypertensive-disorders-of-pregnancy–fetal-growth-restriction group showed significantly lower cardiac output and increased compared with those in the control group. These values were associated with concentric remodeling of the left ventricle owing to relatively increased wall thickness, which was not accompanied by an increase in left ventricular mass. Isolated fetal growth restriction presented similar but less important hemodynamic changes; however, there was no change in relative wall thickness. At postpartum follow-up, the hemodynamic parameters of women in the hypertensive-disorders-of-pregnancy–fetal-growth-restriction and isolated-fetal-growth-restriction groups reverted to values similar to those of the control group. Only 8.3% of women in these groups experienced hypertension even in the postpartum period, and asymptomatic stage-B cardiac failure was observed for 17% at echocardiography. In the group of women with hypertensive disorders of pregnancy and appropriate for gestational age fetuses, cardiac output increased as in normal pregnancies, but total vascular resistance was significantly higher; hypertension then occurred, along with ventricular concentric hypertrophy and diastolic dysfunction. At postpartum follow-up, women in the hypertensive-disorders-of-pregnancy–appropriate-for-gestational-age-fetus group showed significantly higher mean arterial pressure, total vascular resistance, and left ventricular mass compared with those in the control group. Persistent hypertension and asymptomatic stage-B cardiac failure were observed in 39.1% and 13% of women in the former group, respectively.

CONCLUSION: Pregnancies with hypertensive disorders of pregnancy and fetal growth restriction and normotensive pregnancies with fetal growth restriction were associated with the hemodynamic profile of lower heart rate and cardiac output, most likely because of abnormal adaptation to pregnancy, as confirmed by abnormal changes from pregnancy to the postpartum period. The heart rates and cardiac output of women in the hypertensive-disorders-of-pregnancy–appropriate-for-gestational-age-fetus group showed changes opposite to those observed in the hypertensive-disorders-of-pregnancy–fetal-growth-restriction and fetal-growth-restriction groups. Obesity and other metabolic risk factors, significantly prevalent in women in the hypertensive-disorders-of-pregnancy–appropriate-for-gestational-age-fetus group, predispose to hypertension and cardiovascular diseases during pregnancy and the postpartum period, potentially offering a window for personalized prevention. Such preventive strategies could differ in women with hypertensive disorders of pregnancy and fetal growth restriction characterized by poor early placental development.

Key words: cardiac output, cardiac remodeling, diastolic function, left ventricle remodeling, left ventricular mass, preeclampsia, total vascular resistances

Introduction

Major maternal cardiovascular changes occur during pregnancy to adapt to the increasing demands of the fetolacental unit.[1] As early as 1 to 2 weeks after conception, maternal circulation turns into a hyperdynamic system with increased plasma volume, heart rate (HR), cardiac output (CO), and arterial and venous compliance resulting in decreased mean arterial pressure (MAP) and total vascular resistance (TVR).[2,3] Myocardial hypertrophy also occurs with unchanged wall thickness-to-cavity ratio.[2,3]

Two major clinical phenotypes of hypertensive disorders of pregnancy (HDP) can affect pregnant women.[4] One form, more severe and rare, is associated with early placental insufficiency, abnormal uterine artery Doppler velocimetry, and reduced plasma concentrations of proangiogenic factors, frequently resulting in fetal growth restriction (FGR) and eventually in maternal hypertension and organ damage.[5,6] The second form is much

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AJOG MFM at a Glance

Why was this study conducted?

The hemodynamics and cardiac remodeling during pregnancy and the postpartum period in women with hypertensive disorders of pregnancy (HDP) could be different in cases with fetal growth restriction (FGR) and appropriate for gestational age (AGA) fetuses, regardless of gestational age at onset.

Key findings

Women with FGR had hemodynamic profiles with low cardiac output and high vascular resistance. At 40 weeks postpartum, these values returned to normal.

Women with HDP and AGA fetuses, characterized by higher body mass index and metabolic complications, showed a normal adaptation to pregnancy with regard to cardiac output; however, they had higher peripheral resistance, increased left ventricular mass, and diastolic dysfunction. These indices remained significantly higher in the postpartum period.

What does this add to what is known?

The assessment of hemodynamic profile in women with HDP may lead to different therapeutic strategies in pregnancy and tailored preventive interventions for reducing cardiovascular diseases in later life.

more common, usually presents with late-onset hypertension, normal fetal growth, and late placental damage, and is frequently associated with maternal metabolic syndrome.[7−13]

In comparison with uncomplicated pregnancies, higher TVR and lower CO have been described in early-onset HDP and HDP with FGR.[3,14−20] Pregnancies with early FGR share the same hemodynamic profile with early-onset preeclampsia, except for the TVR, which is not high enough to determine a blood pressure above the normal thresholds.[21−24] These changes may persist in the postpartum period and lead to increased life-long cardiovascular risk.[10,25−28]

Conversely, women with late-onset HDP with appropriate for gestational age (AGA) fetuses show a different hemodynamic profile during pregnancy[13,14] and in the postpartum period.[25,27] They have a hyperdynamic circulation with high CO, which is directly proportional to the body mass index (BMI) and normal or elevated HR,[13] whereas apparently contradictory data have been reported on TVR.[13,29] Indeed, these data could be the results of difference in gestational age, late assessment of hemodynamics, associated FGR, or the coexistence of obesity. High CO associated with high venous pressure can elicit endothelial damage and increase in TVR. Similarly, bimodal fetal weight distribution in late preeclampsia could explain the high TVR and low CO observed in a minority of cases of late preeclampsia with FGR.[13,24] Indeed, preexisting metabolic risk factors for endothelial dysfunction and low-grade inflammation in association with obesity have often been reported in these women.[11,12]

On the basis of these reported data,[1−31] we hypothesize that the hemodynamic and cardiovascular features observed in women with HDP and in the postpartum period are better explained by their association with either FGR or AGA fetuses, regardless of gestational age at onset.

We analyzed maternal hemodynamic profile during pregnancy and at 6 to 12 months postpartum in women with HDP with or without FGR, in normotensive women with FGR, and in women with uncomplicated pregnancies.

Materials and Methods

Setting and type of study

This was a prospective longitudinal case−control study, conducted between January 2018 and March 2020 at the Department of Obstetrics and Gynecology, Ospedale Maggiore Policlinico, University of Milan, a tertiary referral hospital, in collaboration with the Unit of Cardiology of Vittore Buzzi Children's Hospital, Milan. The study was approved by the local institutional review committee (EC Niguarda-Nord Milano N° 10818). Written informed consent was obtained from all participants.

Participants

Women with singleton pregnancy complicated with HDP and AGA fetuses, HDP, and/or FGR were recruited consecutively both in the outpatient clinic at diagnosis and among the hospitalized patients. Patients with chronic hypertension, preexisting diabetes mellitus, thrombophilia, cardiac malformations, diseases such as heart failure and coronary disease, chromosomal abnormalities, congenital infections, congenital malformations, conception with in vitro fertilization, and age <18 years were excluded. Patients were subsequently classified into 3 groups: HDP-AGA fetus, HDP-FGR, and FGR. The group allocation was confirmed at the end of pregnancy. Recruitment continued until the calculated sample size was reached in each group.

An equivalent number of patients with uncomplicated pregnancies were then enrolled as controls during their antenatal visit and considered eligible only after an uneventful perinatal outcome. Two control patients were excluded because of diagnoses of protein C deficiency and fetal malformation, respectively. Two additional control patients delivered in a different hospital and were therefore excluded because of lack of data.

The definition of HDP was made according to the International Society for the Study of Hypertension in Pregnancy Guidelines,[32] with the exclusion of chronic hypertension. The published Delphi criteria were adopted for the definition of FGR.[33]

Study design and follow-up

The following data were recorded at enrollment: maternal age, ethnicity, BMI, parity, smoking, known chronic diseases, and obstetrical history.

Gestational age was calculated from the crown−rump length measured at the first-trimester ultrasound.[34]

At recruitment, an experienced sonologist examined fetal biometry and Doppler velocimetry to calculate: the umbilical artery pulsatility index (PI), the middle cerebral artery PI, and the mean uterine artery PI.[3,6] Cerebral placental ratio was calculated. Abdominal circumference percentiles were calculated on the basis of local-standard charts.[35]

Delivery mode and perinatal outcome data were recorded. Major and minor complications were defined in Supplemental Table 1.

Echocardiography

Maternal hemodynamic monitoring was performed at recruitment and in the post partum at a median gestational age of 32 week (interquartile range [IQR], 24 −40), and after delivery by a dedicated cardiologist, blinded to maternal data. Transthoracic 2-dimensional imaging and M-mode and Doppler measurements were obtained according to the European and American guidelines[36,37] with the patient at rest and in left lateral decubitus position by iE33 (Philips Healthcare, Bothell, WA).

Data were acquired from the standard views. For each acquisition, noncompressed data of 3 cardiac cycles were stored in a cine-loop format and analyzed offline to obtain the conventional and tissue Doppler indices.

Maternal height, weight, and brachial blood pressure were obtained at the same time. Blood pressure measurements were obtained in a semirecumbent position, using an appropriately sized cuff and an automatic device validated for pregnant patients (Omron M7; White Medical, Rugby, United Kingdom). MAP was then calculated. The HR was evaluated simultaneously using an electrocardiogram.

Asymptomatic stage-B cardiac failure was defined as wing: left ventricular hypertrophy (left ventricular mass [LVM] index >95 g/m^2), left ventricular concentric remodeling (LVM index >95 g/m^2 and relative wall thickness >0.42 cm), mild left ventricular systolic dysfunction (ejection fraction >40% but <55%), or asymptomatic valve pathology.

Statistical analysis

Univariable analysis was carried out using parametric and nonparametric tests after identifying normally and nonnormally distributed data with the Kolmogorov−Smirnov test. Data were expressed as mean±standard deviation, as median and IQR, or as absolute number with percentage. Analysis of variance, Kruskal−Wallis, Student *t* test, and chi-square test, followed by Dunnett post hoc test or Marascuilo procedure were used to assess the differences among study groups. Statistical significance was considered as *P* value <.05.

Hemodynamic data were compared during pregnancy and the postpartum period as cross-sectional data. Echocardiography was performed once or at most twice at different gestational ages, depending on the timing of diagnosis.

Multivariable analysis was then performed with a general linear model (GLM) for repeated measures stratified by the 4 groups. The effect of covariates was also evaluated for each hemodynamic variable. The estimated values were expressed as percentage of variation using the values of controls observed in pregnancy and at follow-up as the reference. Therefore, the controls always scored the value of 0 in both pregnancy and the puerperium. To detect differences in hemodynamic variables between controls and each of the 3 groups of interest, a contrast analysis was also conducted.

Results

Demographic and clinical data

A total of 228 consecutive patients were recruited. Two patients were excluded for minor fetal congenital malformations; 6 patients were lost to follow-up at delivery. The remaining 220 patients were eligible for the analysis during pregnancy; 36 were classified as cases of HDP-AGA fetus, 49 as HDP-FGR, 92 as FGR, and 43 as controls.

Demographic characteristics are shown in Table 1. Women with HDP-AGA fetuses were older, had the highest prepregnancy BMI, were first diagnosed at a significantly advanced gestational age, and had the highest percentage of coexisting gestational diabetes mellitus. The prevalence of family history of hypertension was significantly lower in women with FGR only.

Table 2 shows the sonographic measurements. Women with HDP-FGR had a significantly higher uterine artery PI than those with FGR, those with HDP-AGA fetuses, and controls. The umbilical artery PI, as expected, was significantly higher in women with HDP-FGR or FGR. Similarly, the cerebroplacental ratio was significantly lower in women with HDP-FGR or FGR.

Table 3 shows the perinatal outcomes. HDP-FGR and FGR had the worst perinatal outcomes; the highest cesarean delivery rate and the lowest gestational age at delivery were observed in the HDP-FGR group.

Univariable analysis of maternal hemodynamics

Hemodynamics during pregnancy. Echocardiography was performed in 176 of 220 (80%) patients during pregnancy, and forgone for the remaining 44 (20%) patients because of patient refusal, clinical emergencies that made the examination impossible, or the cardiologist being unavailable if patient recruitment occurred on the day of indicated delivery.

Table 4 shows major maternal hemodynamic parameters during pregnancy (all recorded data are reported in Supplemental Table 1). HR and CO were significantly lower in women in the HDP-FGR and FGR groups compared with those in the HDP-AGA fetus group and controls. TVR was the highest in patients with HDP-FGR and the lowest in controls, whereas the HDP-AGA fetus and FGR groups showed intermediate values, which were nevertheless significantly higher in the FGR group than in controls. Indices of cardiac remodeling, LVM, and relative wall thickness were the highest in women with HDP and AGA fetuses. The HDP-FGR group had significantly higher LVM than the normotensive FGR

TABLE 1
Demographic and clinical characteristics of the 3 study groups and controls

Variable	Controls n=43	HDP-AGAf n=36	HDP-FGR n=49	FGR n=92	*P* value[a]	Post hoc test
Maternal age (y)	32.7±5.5	35.3±4.5	33.6±5.8	31.8±5.5	.007[a]	[b]
Family history of hypertension	62.2% (23)	71.9% (23)	66% (31)	38.4% (33)	.001[a]	[c,d]
Nulliparous women	65.1% (28)	58.3% (21)	69.4% (34)	63% (58)	.8	
Previous HDP/FGR	2.3% (1)	25% (9)	12.2% (6)	14.1% (13)	.03[a]	[e]
Prepregnancy BMI (kg/m^2)	21.9 (19.5–24.6)	26.4 (24.0–31.1)	23.5 (21.0–25.9)	21.4 (19.1–24.1)	<.001[a]	[b,d,e]
Weight gain during pregnancy (kg)	11.0 (8.5–13.0)	12.0 (9.0–19.0)	10.0 (7.0–12.8)	11.0 (8.0–13.0)	.03[a]	[c]
Smoking habit	7.5% (3)	3% (1)	6.3% (3)	13.6% (12)	.2	
Obstetrical complications (including gestational diabetes mellitus, hypothyroidism, cholestasis)	9.3% (4)	61.1% (22)	38.8% (19)	17.4% (16)	<.001[a]	[b,e,f]
Gestational diabetes mellitus	0% (0)	25% (9)	10.2% (5)	3.3% (3)	<.001[a]	[b,e]
Gestational age at diagnosis and recruitment (wk)	31.7±3.9	36.6±2.9	31.6±4.0	32.3±4.8	<.001[a]	[b,c,e]

Data are expressed as mean±standard deviation, as median and interquartile range, or as absolute number with percentage, as appropriate.

AGAf, appropriate for gestational age fetus; *BMI*, body mass index; *FGR*, fetal growth restriction; *HDP*, hypertensive disorders of pregnancy.

[a] Analysis of variance, Kruskal–Wallis, or chi-square test, as appropriate. Dunnett post hoc test or Marascuilo procedure was used to assess differences among and between generated groups. Statistical significance was reached with *P*<.05; [b] *P* value <.05 for FGR vs HDP-AGAf; [c] *P* value <.05 for FGR vs HDP-AGAf; [d] *P* value <.05 for FGR vs HDP-FGR; [e] *P* value <.05 for controls vs HDP-AGAf; [f] *P* value <.05 for controls vs HDP-FGR.

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group, whose LVM was same as that of controls. Among indices of diastolic function, 62% of women with HDP and AGA fetuses presented E'/A' <1, suggesting altered diastolic relaxation.

Hemodynamics at postpartum follow-up. The median time of postpartum echocardiography was 32 weeks (IQR, 24–40) after delivery. It was performed in 104 of 220 patients (47%); the remaining patients were lost to follow-up. Major hemodynamic data are summarized in Table 5 (all recorded data are reported in Supplemental Table 2). Patients in the HDP-AGA fetus group

TABLE 2
Ultrasound and Doppler velocimetry parameters of the study groups

Variable	Controls n=43	HDP-AGAf n=36	HDP-FGR n=49	FGR n=92	*P* value[a]	Post hoc test
AC percentile at recruitment	50.0 (30.0–68.0)	57.5 (36.0–90.0)	3.0 (2.0–6.5)	4.0 (3.0–6.8)	<.001[a]	[b,c,d,e]
Mean UtA-PI >95th pc	4.7% (2)	25.7% (9)	67.3% (33)	34.1% (31)	<.001[a]	[b,c,d,f]
Mean UtA-PI	1.03±0.22	1.46±0.60	1.94±0.60	1.49±0.63	<.001[a]	[b,c,d,f,g]
UA-PI>95th pc	0% (0)	0% (0)	32.7% (16)	19.8% (18)	<.001[a]	[b,c,d,e]
UA-PI	0.99±0.18	1.03±0.25	1.29±0.52	1.21±0.28	<.001[a]	[b,c,d,e]
MCA-PI	1.03±0.18	0.96±0.23	0.90±0.32	0.95±0.26	.130	
CPR	1.12±0.29	1.06±0.32	0.82±0.35	0.90±0.37	<.001[a]	[b,c,d]
CPR <1	0% (0)	3.2% (1)	30.6% (15)	18.7% (17)	<.001[a]	[b,c,d,e,f]

Data are expressed as mean±standard deviation, as median and interquartile range, or as absolute number with percentage, as appropriate. PI of Doppler parameters and CPR are expressed in multiples of the median.

AC, abdominal circumference; *AGAf*, appropriate for gestational age fetus; *CPR*, cerebroplacental ratio; *FGR*, fetal growth restriction; *HDP*, hypertensive disorders of pregnancy; *MCA*, middle cerebral artery; *pc*, percentile; *PI*, pulsatility index; *UA*, umbilical artery; *UtA*, uterine artery.

[a] Analysis of variance or chi-square test, as appropriate. Dunnett post hoc test or Marascuilo procedure was used to assess differences among and between generated groups. Statistical significance was reached with *P*<.05; [b] *P* value <.05 for controls vs HDP-FGR; [c] *P* value <.05 for controls vs FGR; [d] *P* value <.05 for HDP-AGAf vs HDP-FGR; [e] *P* value <.05 for HDP-AGAf vs FGR; [f] *P* value <.05 for HDP-FGR vs FGR; [g] *P* value <.05 for controls vs HDP-AGAf.

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TABLE 3
Perinatal outcomes of the study groups

Variable	Controls n=43	HDP-AGAf n=36	HDP-FGR n=49	FGR n=92	*P* value[a]	Post hoc test
Gestational age at delivery (wk)	40.0 (39.0–41.0)	38.6 (37.2–39.3)	34.0 (30.2–36.9)	38.4 (36.0–39.1)	<.001[a]	b,c,d,e,f
Percentile of birthweight	50.0 (25.0–76.0)	48.0 (25.5–71.5)	5.0 (2.5–10.0)	4.0 (2.0–8.0)	<.001[a]	c,d,e,g
Mode of delivery: cesarean delivery	18.6% (8)	41.7% (15)	83.7% (41)	42.9% (39)	<.001[a]	c,d,e,f
Apgar 5'	10±0.3	9±0.8	9±1.2	9±1.2	<.001[a]	c,e,f
-BE	5.14±3.03	4.24±3.00	3.28±3.83	3.66±2.79	.04[a]	
Fetoplacental ratio	6.7±0.7	6.0±0.7	4.5±2.7	6.2±1.1	.2	
Admission to NICU	0% (0)	8.3% (3)	62.5% (30)	26.1% (23)	<.001[a]	c,d,e,f
Neonatal complications	9.3% (4)	33.3% (12)	72.1% (31)	32.6% (28)	<.001[a]	c,d,e,f
Perinatal death	0% (0)	0% (0)	10.2% (5)	2.2% (2)	.1	

Data are expressed as mean±standard deviation, as median and interquartile range. or as absolute number with percentage.

AGAf, appropriate for gestational age fetus; *-BE*, minus base excess; *FGR*, fetal growth restriction; *HDP*, hypertensive disorders of pregnancy; *NICU*, neonatal intensive care unit.

[a] Analysis of variance, Kruskal–Wallis, or chi-square test, as appropriate. Dunnett post hoc test or Marascuilo procedure was used to assess differences among and between generated groups. Statistical significance was reached with $P<.05$; [b] *P* value <.05 for controls vs HDP-AGAf; [c] *P* value <.05 for controls vs HDP-FGR; [d] *P* value <.05 for controls vs FGR; [e] *P* value <.05 for HDP-AGAf vs HDP-FGR; [f] *P* value <.05 for HDP-FGR vs FGR; [g] *P* value <.05 for HDP-AGAf vs FGR.

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showed the highest BMI and a significantly higher rate of obesity at 6 to 12 months postpartum (74%). MAP remained significantly higher in the group with HDP and AGA fetuses than in the FGR and control groups. Hypertension persisted at 6 to 12 months postpartum in 39.1% of the HDP-AGA fetus group and 8.3% of the HDP-FGR group. LVM remained significantly higher in the HDP-AGA fetus group than in the FGR group. Asymptomatic

TABLE 4
Maternal hemodynamic parameters during pregnancy

Variable	Controls n=27/43	HDP-AGAf n=30/36	HDP-FGR n=41/49	FGR n=78/92	*P* value[a]	Post hoc test
MAP (mm Hg)	83.6±8.7	102.6±9.3	100.9±9.5	86.3±8.7	<.001[a]	b,c,d,e
HR (bpm)	81.9±9.8	85.1±16.2	71.1±11.5	75.5±12.1	<.001[a]	c,d,f,g
Hemodynamic parameters						
CO (L/min)	5.4±0.9	5.3±1.2	4.4±0.9	4.5±1.0	.04[a]	c,f,g
TVR (dyn·s·cm^{-5})	1179.9±249.3	1542.4±339.7	1794.4±350.8	1414.6±324.8	<.001[a]	b,c,e,f,g
Indexes of left ventricular remodeling						
LVM (g)	126.3±22.7	165.2±39.0	136.4±26.1	121.0±18.7	<.001[a]	b,d,e,g
RWT (cm)	0.35±0.03	0.40±0.09	0.38±0.05	0.36±0.04	.001[a]	b,c
Index of diastolic function						
E'/A'	1.2±0.4	0.9±0.3	1.2±0.3	1.3±0.4	<.001[a]	b,d,g
Left ventricular function						
Impaired diastolic relaxation (E'/A')	37% (10)	62.1% (18)	29.3% (12)	19.5% (15)	<.001[a]	d,g

Data are expressed as mean±standard deviation, as median and interquartile range, or as absolute number with percentage.

AGAf, appropriate for gestational age fetus; *CO*, cardiac output; *FGR*, fetal growth restriction; *HDP*, hypertensive disorders of pregnancy; *HR*, heart rate; *LVM*, left ventricular mass; *MAP*, mean arterial pressure; *RWT*, relative wall thickness; *TVR*, total vascular resistance.

[a] Analysis of variance. Post hoc Dunnett test was used to assess differences among and between generated groups. Statistical significance was reached with $P<.05$; [b] *P* value <.05 for controls vs HDP-AGAf; [c] *P* value <.05 for controls vs HDP-FGR; [d] *P* value <.05 for HDP-AGAf vs FGR; [e] *P* value <.05 HDP-FGR vs FGR; [f] *P* value <.05 for controls vs FGR; [g] *P* value <.05 for HDP-AGAf vs HDP-FGR.

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TABLE 5

Demographic characteristics and hemodynamic parameters at a median of 32 weeks (interquartile range, 24–40) after delivery

Variable	Controls n=17/43	HDP-AGAf n=23/36	HDP-FGR n=24/49	FGR n=40/92	*P* value[a]	Post hoc test
Time from delivery (mo)	8.0 (6.3–11.1)	9.0 (6.2–10.0)	7.9 (6.5–10.8)	7.9 (6.2–9.8)	.8	
Postpartum BMI (kg/m^2)	22.2 (19.5–24.8)	28.0 (23.5–32.7)	23.5 (21.9–27.7)	22.3 (19.6–24.3)	<.001[a]	b,c
Postpartum BMI ≥25 kg/m^2	23.5% (4)	73.9% (17)	33.4% (8)	17.5% (7)	<.001[a]	b,c,d
Hemodynamic parameters						
MAP (mm Hg)	82.9±8.4	99.0±13.5	90.1±8.7	85.7±7.7	<.001[a]	b,c,d,e
Hypertension	0% (0)	39.1% (9)	8.3% (2)	5% (2)	<.001[a]	b,c,d
HR (bpm)	71.8±7.1	72.8±11.9	76.0±9.5	70.3±10.2	.2	
SV (mL)	59.6±10.0	62.4±13.9	56.3±10.8	58.5±8.8	.3	
CO (L/min)	4.2±0.5	5.0±1.1	4.4±0.8	4.0±0.7	.180	
TVR (dyn·s·cm^{-5})	1490±217	1765±499	1632.2 ±401	1636 ±286	.1	
Indexes of left ventricular remodeling						
LVM (g)	112.8±20.7	132.8±26.9	118.3±18.9	111.4±14.6	.001[a]	b,c
RWT (cm)	0.35±0.03	0.36±0.04	0.37±0.03	0.36±0.03	.6	
Index of diastolic function						
E'/A'	1.3±0.4	1.3±0.3	1.4±0.3	1.4±0.4	.5	
Left ventricular function						
Impaired diastolic relaxation (E'/A'<1)	17.6% (3)	21.7% (5)	16.7% (4)	12.5% (5)	.8	

Data are expressed as mean ± standard deviation, as median and interquartile range or as absolute number with percentage.

AGAf, appropriate for gestational age fetus; *BMI*, body mass index; *CO*, cardiac output; *FGR*, fetal growth restriction; *HDP*, hypertensive disorders of pregnancy; *HR*, heart rate; *LVM*, left ventricular mass; *MAP*, mean arterial pressure; *RWT*, relative wall thickness; *SV*, stroke volume; *TVR*, total vascular resistance.

[a] Analysis of variance, Kruskal–Wallis, or chi-square test, as appropriate. Dunnett post hoc test or Marascuilo procedure was used to assess differences among and between generated groups. Statistical significance was reached with *P*<.05; [b] *P* value <.05 for controls vs HDP-AGAf; [c] *P* value <.05 for HDP-AGAf vs FGR; [d] *P* value <.05 for HDP-AGAf vs HDP-FGR; [e] *P* value <.05 for controls vs HDP-FGR.

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stage-B cardiac failure was observed in 13%, 17%, and 10% of women in the HDP-AGA fetus, HDP-FGR, and FGR groups, respectively.

An improvement in myocardial relaxation with a significant increase of E'/A' ratio was observed in all groups.

Multivariable longitudinal comparison of pre- and postpartum data. Longitudinal data of 104 patients were available. The Figure shows the longitudinal changes of MAP, HR, CO, TVR, LVM, and E'/A' ratio, adjusted for available significant covariates, from pregnancy to 40 weeks postpartum, expressed in percentage deviations from data observed in controls, to whom the value of 0 was assigned at any time of observation. Among the affected groups, the highest degree of deviation of hemodynamic data from normal was observed at the time of delivery.

Mean arterial pressure. Patients in the HDP-AGA fetus group had the highest values at delivery, which remained significantly higher at the end of follow-up (*P*<.001). In the other 2 groups, adjusted MAP returned to values not significantly different from those of controls.

Cardiac output. Patients in the HDP-FGR and FGR groups had lower values compared with the control group throughout pregnancy, but in women with HDP and AGA fetuses, CO was not different from that of the controls.

Total vascular resistance. Patients in the HDP-FGR group showed significantly higher values (*P*<.001). TVR dropped in all groups at follow-up but remained higher in patients in the HDP-AGA fetus group (*P*<.001). This characteristic and the high nonadjusted CO explained the significantly higher MAP observed in these patients.

Left ventricular mass and E'/A' ratio. Patients in the HDP-AGA fetus group showed significantly higher LVM and significantly lower adjusted longitudinal values of E'/A' (*P*<.001).

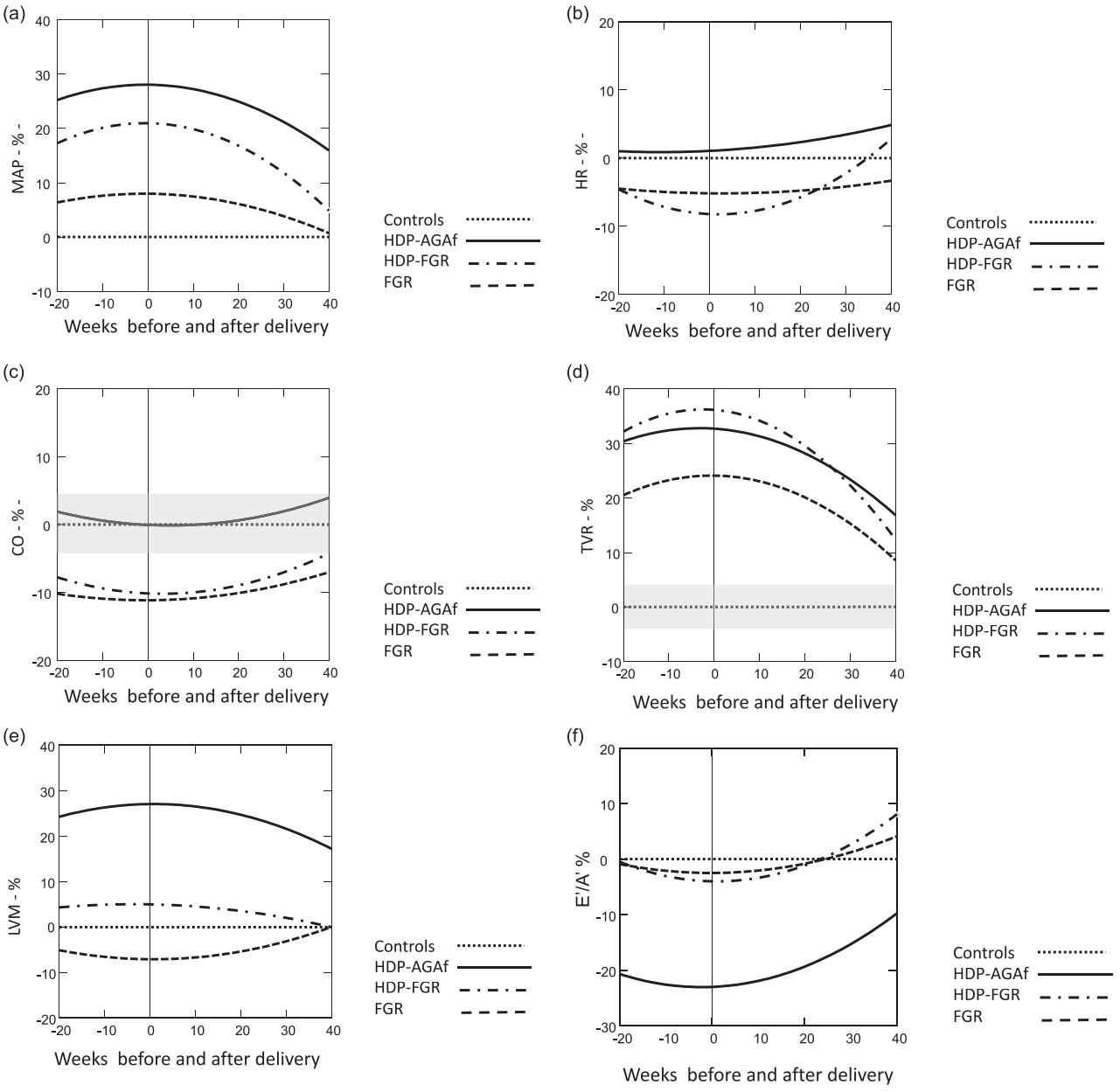
Discussion

Principal findings

Patients affected by hypertensive disorders, stratified according to their association with FGR or AGA fetuses, or FGR without clinical hypertension showed significantly different clinical characteristics, Doppler velocimetry, perinatal outcomes, and pre- and postpartum maternal hemodynamics.

FIGURE

Hemodynamic changes during pregnancy and post-partum



Estimated percentage of variation for MAP, HR, CO, TVR, LVM, in the HDP-AGA fetus, HDP-FGR, and isolated FGR groups compared with controls from the onset of disease until 9 months of the puerperium.

In the X-axis, the "0" value represents time of delivery. In the Y-axis, the percentage of variation for controls is always 0.

AGAf, appropriate for gestational age fetus; *CO*, cardiac output; *FGR*, fetal growth restriction; *HDP*, hypertensive disorders of pregnancy; *HR*, heart rate; *LVM*, left ventricular mass; *MAP*, mean arterial pressure; *TVR*, total vascular resistance.

Di Martino. Maternal pre- and postpartum hemodynamic profile. Am J Obstet Gynecol MFM 2022.

Results in the context of what is known

In the light of previous[7,11,13] and recent[4,38] interpretations of the pathogenesis of the 2 main phenotypes of HDP,[3] we stratified patients into those with associated FGR and those with AGA fetuses. Our findings, independently from gestational age at diagnosis, suggest that preexisting metabolic risk factors such as obesity play a crucial role in the development of

hypertension when late oxidative stress of the placenta converges with endothelial damage caused by maternal predisposing risk factors.[4,10,13,39] Indeed, the presence of preexisting endothelial dysfunction and low-grade inflammation adding to placental syncytiotrophoblast oxidative stress caused by late villous crowding and decidual atherosis[6] may explain maternal hypertension without early placental involvement[4,8] and thus without FGR.

At the GLM analysis, a BMI >25 resulted as an independent factor in determining hemodynamic changes. The similar CO between women with HDP and AGA fetuses and controls suggests that there is no early maternal maladaptation to pregnancy. However, the highest values of LVM and relative wall thickness found in the HDP-AGA fetus group suggest that maternal heart overload is determined not only by systemic hypertension, but also by a higher BMI, leading to abnormal cardiac remodeling with concentric hypertrophy. This is also supported by the high percentage of women with impaired diastolic relaxation.

The BMI should be considered as an independent factor, as already reported by our group,[13] Zandstra et al,[18] and Ling et al.[40] The finding of persistently increased BMI, MAP, and LVM in the postpartum period, despite the return to normal HR and decreased CO, supports this view. These findings agree with both short-[25,41,42] and long-term[27] follow-up studies and support the hypothesis of persistent endothelial dysfunction related to metabolic syndrome,[43,44] superimposed to placental stress, underlining the importance of prevention in these women for future pregnancies and cardiovascular disease later in life.[45]

Data on TVR in women with HDP and AGA fetuses are apparently contradictory relative to the reported cohorts. In 2008, Valensise et al[13] described late-onset HDP as a hemodynamic preclinical state with high CO and low TVR. These findings were confirmed by Lees et al,[29,46] whereas Melchiorre et al[15] found high CO and TVR in term preeclampsia, in a cohort predominantly associated with AGA fetuses. A possible explanation may be that in the preclinical phase, women with HDP and AGA fetuses show normal adaptation associated with low TVR, whereas in the clinical phase, because of volume overload and endothelial damage,[47] a shift toward increased TVR occurs. In our study, 75% of women with HDP and AGA fetuses were recruited from 37 weeks of gestation onward. The late gestational age and the combined effect of maternal low-grade inflammation and circulating cytokines produced by venous endothelial damage may explain the TVR >1500 dyn/s/cm^{-5} observed in half of the women in this group.

The HDP-FGR and FGR groups were mostly characterized by abnormal feto-maternal Doppler velocimetry, a known proxy of early placental insufficiency.[48−50] Significantly higher TVR and lower CO indicate HDP with FGR and FGR in both the preclinical[14] and clinical[29,51,52] phases of the disease. An abnormal hemodynamic adaptation to pregnancy was found at as early as 5 to 7 weeks of gestation in women who subsequently developed FGR.[53] This evidence suggests that both maternal cardiovascular maladaptation and impaired placental maturation may play a role in developing HDP with FGR or FGR.[54−56] The observation of no change in CO from pregnancy to the postpartum period[10,17] supports this hypothesis.

The HDP-FGR group showed a concentric cardiac remodeling that may explain the development of postpartum asymptomatic stage-B cardiac failure in 17% of cases in this group. This remains a controversial area in which classification criteria and early antihypertensive treatment may play a confounding role.[41,42]

Strength and limitations

The strength of our study was the consecutive "clinical-real-life" design.

Moreover, maternal echocardiography was performed by a single blinded cardiologist at recruitment before antihypertensive therapy. Echocardiography allows the evaluation of some parameters that cannot be assessed with other biophysical tools such as cardiac remodeling, indices of ventricular dysfunction, and stages of cardiac failure.

Our study has some limitations. The control group was not matched for gestational age at examination with the HDP-FGR group. However, in uncomplicated pregnancies, CO and TVR reach a plateau at the end of the second trimester.[2] Thus, differences in the echocardiographic findings should not depend on gestational age at which the examination was performed.

We did not correct absolute hemodynamic values for maternal BMI. This is a controversial area because body mass in pregnancy is altered by pregnancy volume itself and even by the variation in fat tissue metabolism according to postprandial or fasting state. However, BMI was included in the GLM multivariate analysis.

TVR was higher in the HDP-FGR group during pregnancy but remained higher in the postpartum in the HDP-AGA fetus group. The corrected indexed data are provided in the supplemental tables. Patients were recruited both in the outpatient clinic and during hospitalization; these latter cases were more likely to be severe conditions requiring more frequent controls, contributing to a mixture of cases of different severity in the study population. This introduces selection bias, but this population represents our real-life clinical setting, where we observed the value of maternal hemodynamic assessment along the entire spectrum of severity of these clinical phenotypes.

Twenty percent of eligible women did not undergo echocardiography, and approximately <60% were lost to follow-up at 24 to 40 weeks postpartum. These echocardiographies were not performed because of clinical emergencies that made the examination impossible, unavailability of the cardiologist, or patient refusal. However, although this may have introduced selection bias, high dropout rates are common in studies such as ours,[57] and this should not prevent comparison of our data with already

known information on the evolution of cardiac function.

Despite these limitations, our findings add robust echocardiographic data to the longitudinal evaluation of patients at 28 to 56 months postpartum.

Clinical and research implications

A thorough hemodynamic assessment of women with HDP with or without FGR may guide different therapeutic strategies in pregnancy[58] and preventive interventions during[59] and after pregnancy.[13] Nitric oxide donors have shown promising results for both prevention and management of HDP and FGR by modifying the alterations in hemodynamic parameters and restoring the optimal maternal cardiac performance.[49,60] Moreover, these findings suggest that hemodynamic assessment, in addition to blood pressure measurement, could be of benefit for personalized prevention of cardiovascular disease in later life for patients with pregnancies affected by HDP with or without FGR.

Conclusions

Pregnancies with HDP and FGR and normotensive pregnancies with FGR were associated with lower HR and CO, which indicated abnormal maternal hemodynamic adaptation to pregnancy, as confirmed by abnormal changes from pregnancy to the postpartum period. Conversely, in predominately at-term women with HDP and AGA fetuses, metabolic risk factors were associated with normal CO, high TVR, higher LVM, and higher proportion of diastolic dysfunction, which persisted in the postpartum period, particularly the high TVR. This indicates a condition of increased metabolic risk and endothelial dysfunction, and thus predisposition to hypertension and cardiovascular disease. ■

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