The "Preeclampsia and Hypertension Target Treatment" study: a multicenter prospective study to evaluate the effectiveness of the antihypertensive therapy based on maternal hemodynamic findings

Elvira di Pasquo, MD; Stefano Raffaele Giannubilo, MD; Beatrice Valentini, MD; Silvia Salvi, PhD; Roberta Rullo, MD; Stefano Fruci, MD; Elisa Filippi, MD; Sara Ornaghi, MD; Sara Zullino, MD; Francesca Rossi, MD; Daniele Farsetti, MD; Daniela Denis Di Martino, PhD; Barbara Vasapollo, MD; Anna Locatelli, MD; Michela De Santis, MD; Andrea Ciavattini, MD; Antonio Lanzone, MD; Federico Mecacci, MD; Enrico Ferrazzi, PhD; Hebert Valensise, MD; Tullio Ghi, PhD

BACKGROUND: Despite major advances in the pharmacologic treatment of hypertension in the nonpregnant population, treatments for hypertension in pregnancy have remained largely unchanged over the years. There is recent evidence that a more adequate control of maternal blood pressure is achieved when the first given antihypertensive drug is able to correct the underlying hemodynamic disorder of the mother besides normalizing the blood pressure values.

OBJECTIVE: This study aimed to compare the blood pressure control in women receiving an appropriate or inappropriate antihypertensive therapy following the baseline hemodynamic findings.

STUDY DESIGN: This was a prospective multicenter study that included a population of women with de novo diagnosis of hypertensive disorders of pregnancy. A noninvasive assessment of the following maternal parameters was performed on hospital admission via Ultrasound Cardiac Output Monitor before any antihypertensive therapy was given: cardiac output, heart rate, systemic vascular resistance, and stroke volume. The clinician who prescribed the antihypertensive therapy was blinded to the hemodynamic evaluation and used as first-line treatment a vasodilator (nifedipine or alpha methyldopa) or a beta-blocker (labetalol) based on his preferences or on the local protocols. The first-line pharmacologic treatment was retrospectively considered hemodynamically appropriate in either of the following circumstances: (1) women with a hypodynamic profile (defined as low cardiac output [≤5 L/min] and/or high systemic vascular resistance [≥1300 dynes/second/cm^2]) who were administered oral nifedipine or alpha methyldopa and (2) women with a hyperdynamic profile (defined as normal or high cardiac output [>5 L/min] and/or low systemic vascular resistances [<1300 dynes/second/cm^2]) who were administered oral labetalol. The primary outcome of the study was to compare the occurrence of severe hypertension between women treated with a hemodynamically appropriate therapy and women treated with an inappropriate therapy.

RESULTS: A total of 152 women with hypertensive disorders of pregnancy were included in the final analysis. Most women displayed a hypodynamic profile (114 [75.0%]) and received a hemodynamically appropriate treatment (116 [76.3%]). The occurrence of severe hypertension before delivery was significantly lower in the group receiving an appropriate therapy than in the group receiving an inappropriately treated (6.0% vs 19.4%, respectively; *P*=.02). Moreover, the number of women who achieved target values of blood pressure within 48 to 72 hours from the treatment start was higher in the group who received an appropriate treatment than in the group who received an inappropriate treatment (70.7% vs 50.0%, respectively; *P*=.02).

CONCLUSION: In pregnant individuals with de novo hypertensive disorders of pregnancy, a lower occurrence of severe hypertension was observed when the first-line antihypertensive agent was tailored to the correct maternal hemodynamic profile.

Key words: hemodynamics, hypertension, pregnancy, therapy

Introduction

Hypertensive disorders of pregnancy (HDPs) represent a leading cause of maternal and perinatal morbidities and mortalities.[1–3] Maintaining strict control of the mother's blood pressure (BP) through proper medication has been shown to enhance pregnancy outcomes.[4–6] Various antihypertensive drugs with different mechanisms of action, such as labetalol, nifedipine, and alpha methyldopa, are accessible to healthcare providers.[7] However, according to a Cochrane review, there is not enough evidence to recommend a specific medication over others.[8]

Recent international guidelines suggest prioritizing the choice of antihypertensive medications based on the clinician's familiarity, the drug's side effects, and the patient's preference.[9–13]

The availability of noninvasive methods to evaluate maternal cardiac function has allowed to show that HDPs may arise in the context of 2 opposite hemodynamic profiles of the patients: one characterized by a reduced cardiac output (CO) and increased systemic vascular resistance (SVR), which is commonly associated with fetal growth restriction (FGR), and the other characterized by a normal or increased CO and reduced SVR, which is commonly associated with normal-sized or large-for-gestational-age fetuses.[14–19] There

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AJOG MFM at a Glance

Why was this study conducted?

This study was conducted to compare the blood pressure (BP) control between pregnant women with de novo hypertension whose first-choice antihypertensive therapy was appropriate or inappropriate by their baseline hemodynamic profile.

Key findings

The use of an antihypertensive therapy tailored to the maternal hemodynamic profile was determined to decrease the occurrence of severe hypertension and to achieve more frequently the target BP values at 48 to 72 hours from the treatment start.

What does this add to what is known?

Our results demonstrate that a tailored pharmacologic intervention aimed at correcting not only the BP values but also the underlying maternal hemodynamic imbalance is more effective in reducing the occurrence of severe hypertension.

is accumulating evidence that, among pregnant patients with hypertension, a more adequate control of BP is achieved when the first given antihypertensive drug is able to correct the underlying hemodynamic disorder of the mother.[20−27] More specifically, in cases where pregnant women have low CO and high vascular resistance, vasodilators seem to be more effective than medications that decrease heart rate or contractility. Conversely, negative inotropes or chronotropes are more appropriate for treating women with hypertension with high CO and low vascular resistance.[25,27,28]

Consequently, we conducted a prospective study with the primary aim of comparing the BP control between patients with de novo hypertension in pregnancy whose first-line antihypertensive therapy was appropriate and patients with de novo hypertension in pregnancy whose first-line antihypertensive therapy was inappropriate by their baseline hemodynamic profile.

Materials and Methods

Study design and study population

The "Preeclampsia and Hypertension Target Treatment" study was a prospective multicentric cohort study conducted from February 2021 to May 2023 across 8 Italian tertiary maternity care centers.

A nonconsecutive series of women with a singleton viable pregnancy between 22 and 38 completed weeks of gestation admitted to one of these units with a diagnosis of new-onset gestational hypertension or preeclampsia (HDPs) and not assuming that antihypertensive therapy was considered eligible for the study purpose.

Here, according to the International Society for the Study of Hypertension in Pregnancy[12] and the American College of Obstetricians and Gynecologists guidelines,[10] gestational hypertension was defined as hypertension arising de novo at ≥20 weeks of gestation in the absence of proteinuria or other symptoms or signs of organ dysfunction. Women with gestational hypertension accompanied by at least one of the following criteria were diagnosed with preeclampsia and enrolled for the study purpose:

1. Proteinuria (defines as a value ≥300 mg per 24 hours or a protein-to-creatinine ratio of ≥0.3 mg/dL)
2. Maternal end-organ dysfunction that includes the following:

- Mild liver involvement (eg, transaminases, alanine aminotransferase or aspartate aminotransferase, > 40 IU/L but less than twice the upper limit of normal concentration) without right upper quadrant or epigastric abdominal pain
- Mild hematological complications (eg, platelet count between 100 and 150,000/μL)
- Acute kidney injury (serum creatinine level ≥1 mg/dL)

3. FGR defined following the Delphi criteria:

- <32 weeks of gestation (early FGR):
  - Abdominal circumference (AC) and estimated fetal weight (EFW) <3rd percentile
  - Absent end-diastolic flow in the umbilical artery (UA)
  - AC or EFW <10th percentile combined with UA pulsatility index (UA-PI) >95th percentile and/or UA-PI >95th percentile
- ≥32 weeks of gestation (late FGR):
  - AC or EFW <3rd percentile or at least 2 out of the following:

- AC or EFW <10th percentile
- AC or EFW crossing more than 2 quartiles; cerebroplacental ratio <5th percentile
- UA-PI >95th percentile[29,30]

Women with severe hypertension (defined as a systolic BP [SBP] of ≥160 mm Hg and/or a diastolic BP [DBP] of ≥110 mm Hg) or those with preeclampsia presenting the following features of severity were not considered eligible for this study[10]: thrombocytopenia (platelet count of $<100 \times 10^9$/L), markedly impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (at least twice the upper limit normal concentration), severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses, and renal insufficiency (serum creatinine concentration >1.1 mg/dL or a doubling of the baseline serum creatinine concentration in the absence of other renal disease or oliguria <500 mL per 24 hours).

The additional exclusion criteria were preexisting hypertension or diabetes mellitus or chronic maternal disease (ie, heart kidney or autoimmune system), smoking or drug addiction, fetal anomalies, intrauterine fetal demise,

suspected impending fetal compromise based on cardiotocography or ultrasound Doppler findings (absent or reversed a-wave in the ductus venosus or reverse end-diastolic flow in the UA), placental abruptio, delivery <48 hours from the admission or any indication to an emergency delivery because of life-threatening maternal morbidity of the central nervous system (eclampsia or posterior reversible encephalopathy syndrome; stroke, transient ischemic attack, or reversible ischemic neurologic deficit; blindness, clonus, severe headaches, or persistent visual scotomata-altered mental status; or Glasgow coma score of <13), cardiorespiratory system (pulmonary edema, need of positive inotropic support, myocardial ischemia or infarction, oxygen saturation <90%, ≥50% inspired oxygen for more than 1 hour, or need of intubation other than cesarean delivery), disseminated intravascular coagulation, or clinical and/or laboratory evidence of hemolysis, elevated liver enzymes, and low platelet level.

Women admitted with preeclampsia below <34 completed weeks of gestation received a course of betamethasone (12 mg intramuscularly every 24 hours for a total of 2 doses) for the induction or acceleration of fetal lung maturity.

Management

On hospital admission, all women who met the inclusion criteria were enrolled in the study using a signed consent form if one of the study investigators was readily available. Before being given any medical treatment (ie, antihypertensive agent or betamethasone), each woman who agreed to be part of the study was submitted by a dedicated operator to a central hemodynamic assessment using USCOM-1A (Ultrasound Cardiac Output Monitor [USCOM]; USCOM Ltd, Sydney, New South Wales, Australia), a noninvasive device employing continuous wave Doppler to obtain velocity time integrals (VTIs) of transaortic or transpulmonary blood flow. Information about CO, stroke volume, and SVR are indirectly obtained through an algorithm combining VTIs, anthropometric parameters (height and weight), and BP values. Measurements were obtained under standardized conditions for the entire cohort.

The USCOM probe was placed in the suprasternal notch to obtain a minimum of 3 consecutive Doppler profiles with the patient in a semirecumbent position. SBP and DBP were recorded following recommendations from the European Society of Hypertension.[31] More specifically, the patients were seated comfortably in a quiet environment for 5 minutes before beginning BP measurements. A standard bladder cuff (12−13 cm wide and 35 cm long) was used for most patients, but larger and smaller cuffs were used for larger (>32 cm) or thinner arms, respectively. The cuff was positioned at the level of the heart, with the back and arm supported to avoid muscle contraction and isometric exercise-dependent increases in BP; phase 1 and 5 (sudden reduction or disappearance) Korotkoff sounds were used to identify SBP and DBP. BP was measured in both arms, and the arm with the higher value was used as the reference. Heart and pulse rates were recorded to exclude arrhythmia.

The clinician who was in charge of the patient and who prescribed the antihypertensive therapy was blinded to the hemodynamic evaluation and used first-line oral antihypertensive drug, either a vasodilator agent (peripherally acting, such as nifedipine 30−60 mg, or centrally acting, such as alpha methyldopa 250−500 mg) or a nonselective beta-blocker (labetalol 100−200 mg), based on the local protocols and on the clinician's experience.[32]

In addition, fetal biometry and Doppler velocimetry were sonographically evaluated at the admission; however, the decision on the type of therapy was not influenced by these data.

According to previous studies,[23,24] the first-line pharmacologic treatment was retrospectively considered hemodynamically appropriate in either of these circumstances:

1. Women with a hypodynamic profile characterized by low CO (≤5 L/min) and/or high SVR (≥1300 dynes/second/cm^2) who were administered oral nifedipine or alpha methyldopa.
2. Women with a hyperdynamic profile characterized by normal or high CO (>5 L/min) and/or low SVR (<1300 dynes/second/cm^2) who were administered oral labetalol.

Maternal BP values were monitored using automated devices every 4 hours since the start of therapy and for the following 72 hours.

The BP values recorded after 24 hours and within 48 to 72 hours since the start of therapy were considered at target if SBP was <140 and ≥130 mm Hg, and DBP was <90 mm Hg and ≥80 mm Hg.[12]

A second-line antihypertensive therapy was added at the discretion of the clinicians of each center if the BP values were not at target after 24 hours from the treatment start.

As for the first-line therapy, this decision was based solely on the clinical response of the patient and not influenced by the USCOM-1A findings.

The obstetrical management of each patient, including the decision on the timing and mode of delivery, was based on the local policy of each center and was not part of a shared clinical protocol. The demographic and clinical features of the study population and the pregnancy and neonatal outcomes were retrieved from the hospital records.

Outcome

The primary outcome of the study was to compare the occurrence of severe hypertension between women treated with a hemodynamically appropriate therapy and women treated with an inappropriate therapy. In addition, the number of patients who achieved target values of BP at 24 to 72 hours from the treatment start was compared between these 2 groups.

The study was approved by the local ethics committee of each center (approval number: 0000201).

Statistical analysis

Statistical analysis was performed using SPSS (version 22; IBM Inc, Armonk,

TABLE 1
Characteristics of included women

Characteristic	N=152
Maternal age (y)	34.0 (30.0–38.5)
Prepregnancy BMI	25.0 (22.0–29.7)
Nulliparous	68 (44.7)
White	98 (64.5)
ART	18 (13.0)
Gestational age at admission	34.1 (32.1–36.6)
Gestational age at delivery	37.4 (35.0–38.3)
Birthweight	2513.0 (1859.0–3000.0)
Birthweight percentile	16.0 (2.4–49.7)
Birthweight of <10th percentile	56 (36.8)
SBP at admission	145.0 (140.0–150.0)
DBP at admission	91.5 (90.0–97.0)

Data are presented as median (interquartile range) or number (percentage).

ART, assisted reproductive technique; *BMI*, body mass index; *DBP*, diastolic blood pressure; *SBP*, systolic blood pressure.

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NY). The Kolmogorov-Smirnov test was used to assess the normality of the distribution of the data. Data were displayed as mean±standard deviation (if normally distributed), median (interquartile range [IQR]) (if nonnormally distributed), or number (percentage) in case of dichotomous variables. Categorical variables were compared using the chi-square or Fisher exact test. Between-group comparison of continuous variables was performed using the *t* test and the Mann-Whitney nonparametric equivalent test. Moreover, 2-sided *P* values were calculated, with *P* values of <.05 considered statistically significant.

Sample size

The sample size was estimated a priori based on an expected prevalence of severe hypertension of approximately 4% in the group receiving a hemodynamic-guided therapy.[23] A 15% incidence of severe hypertension was hypothesized in the group receiving an inappropriate therapy. This would need the enrollment of at least 36 women receiving an inappropriate treatment. The recruitment was stopped when at least 36 women with these characteristics were included.

Results

Throughout the study, a total of 158 women met the inclusion criteria. Of the 158 women, 6 (3.8%) were excluded (2 declined to participate in the study, 2 were intolerant to nifedipine, and 2 had spontaneous labor <48h after admission). A total of 152 women were included in the final analysis, with 116 women (76.3%) receiving a hemodynamically appropriate treatment. The overall characteristics of the study population are shown in Table 1. The Figure shows the distribution of the

FIGURE
Distribution of the included women according to the subtype of hemodynamic pattern at hospital admission (pie chart) and the percentage of women receiving an appropriate treatment for each subtype (histograms)

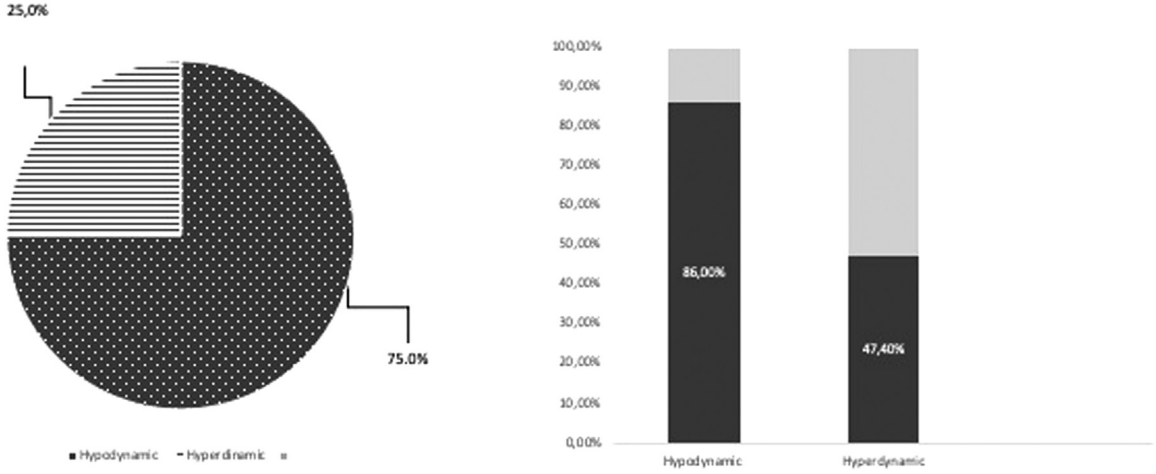

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TABLE 2
Comparison of maternal and obstetric characteristics according to the hemodynamic pattern at admission

Characteristic	Hypodynamic pattern (n=114)	Hyperdynamic pattern (n=38)	*P* value
Maternal age (y)	34.0 (30.0–37.0)	32.0 (31.0–36.4)	.83
Prepregnancy BMI (kg/m^2)	25.7 (22.0–28.5)	24.1 (22.0–29.1)	.63
White	75 (65.8)	23 (60.5)	.56
Gestational weight gain (kg)	9.0 (6.0–12.0)	9.0 (3.8–13.4)	.70
Nulliparous	55 (48.2)	13 (34.2)	.13
ART	15 (13.2)	3 (7.9)	.39
Gestational age at admission (wk)	34.1 (32.1–36.3)	34.0 (31.5–36.6)	.17
Associated IUGR at admission	24 (21.0)	2 (5.2)	.03
Gestational age at delivery (wk)	37.1 (34.4–37.7)	38.1 (36.9–38.7)	.01
Preterm delivery at <34 wk	21 (18.4)	1 (2.6)	.02
Birthweight (g)	2385.0 (1678.0–2908.0)	2963.0 (2581.0–3306.0)	<.001
Birthweight percentile	10.6 (1.5–43.3)	47.0 (20.0–69.9)	<.001
Birthweight of <10th percentile	50 (43.9)	6 (15.8)	.002
Cesarean delivery	55 (48.2)	15 (39.4)	.35
Appropriate treatment	98 (86.0)	18 (47.3)	<.001

Data are presented as median (interquartile range) or number (percentage), unless otherwise indicated.

ART, assisted reproductive technique; *BMI*, body mass index; *IUGR*, intrauterine growth restriction.

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included women according to the subtype of the hemodynamic pattern at hospital admission and the percentage of women receiving an appropriate treatment for each subtype. At the hospital admission, 114 women (75.0%) had a hypodynamic hemodynamic profile, with 98 women (86.0%) receiving an appropriate treatment (18 [18.4%] with alpha methyldopa and 80 [81.6%] with nifedipine). Of the 38 women (25.0%) presenting with a hyperdynamic pattern, 18 (47.4%) were treated with an appropriate therapy (labetalol), whereas 20 (52.6%) were inappropriately given a vasodilator (15 [75.0%] with nifedipine and 5 [25.0%] with alpha methyldopa).

Table 2 shows the comparison of pregnancy and perinatal outcomes between women with a hypodynamic pattern and those with a hyperdynamic pattern.

Compared with women with a hyperdynamic pattern, women with a hypodynamic pattern had a significantly higher incidence of FGR at admission (21.0% [hyperdynamic group] vs 5.2% [hypodynamic group]; *P*=.03) and a significantly higher incidence of delivery at <34 weeks of gestation (18.4% [hyperdynamic group] vs 2.6% [hypodynamic group]; *P*=.02) and a lower gestational age at delivery (37.1 [IQR, 34.4–37.7] vs 38.1 [IQR, 36.9–38.7]; *P*=.01). Moreover, compared with the group of women with a hyperdynamic pattern, the group of women with a hypodynamic pattern had a significantly lower birthweight (2385.0 g [IQR, 1678.0–2908.0] in the hypodynamic group vs 2963.0 g [IQR, 2581.0–3306.0] in the hyperdynamic group; *P*<.001) and birthweight percentile (10.6 [IQR, 1.5–43.3] in the hypodynamic group vs 47.0 [IQR, 20.0–69.9] in the hyperdynamic group; *P*<.001) and a higher incidence of small-for-gestational-age neonates (43.9% in the hypodynamic group vs 15.8% in the hyperdynamic group; *P*=.02).

The occurrence of severe hypertension before delivery was significantly lower in the group of women receiving a hemodynamically appropriate treatment than in the group of women receiving an inappropriate treatment (6.0% vs 19.4%, respectively; *P*=.015) (Table 2). In Table 3, the maternal BP values at follow-up (48–72 hours from the start of therapy) and the clinical evolution of the HDPs are illustrated. The number of women with BP values at target at 48 to 72 hours from the treatment start was higher in the group receiving an appropriate treatment than in the group receiving an inappropriate treatment (70.7% vs 50.0%, respectively; *P*=.02).

The need for a second-line therapy within 48 to 72 hours from the treatment start or before delivery did not vary following the hemodynamic appropriateness of the antihypertensive treatment (19.8% in the appropriate therapy group vs 25.0% in the inappropriate therapy group; *P*=.51).

Discussion

Principal findings

Our findings suggested that, in pregnant women with gestational hypertension or new-onset preeclampsia without severe features, using a first-line antihypertensive treatment tailored to the maternal hemodynamic profile can reduce the occurrence of severe hypertension before delivery. In addition, women who received a hemodynamically appropriate therapy were more likely to reach target BP values within 48 to 72 hours of starting treatment.

Results in the context of what is known

Our data seem to support the results from recent studies,[22–26] demonstrating that, among women with HDPs, a tailored pharmacologic intervention directed not only to lower the BP values but also to correct the underlying hemodynamic imbalance yields a tighter control of the BP and reduces the risk of severe maternal complications.

More in detail, when the occurrence of hypertension in pregnancy is associated with a hypodynamic profile of the mother (lower CO and increased SVR),

TABLE 3
Maternal hemodynamics findings, blood pressure values at follow-up (48–72 hours), and pregnancy outcome according to therapy appropriateness

Variable	Appropriate (n=116)	Inappropriate (n=36)	*P* value
Baseline SBP (mm Hg)	145.0 (140.0–150.0)	140.0 (140.0–153.0)	.52
Baseline DBP (mm Hg)	92.0 (90.0–96.0)	90.0 (90.0–99.0)	.86
Mean SBP (mm Hg) at follow-up	133.0 (130.0–137.0)	135.0 (130.0–145.0)	.09
Mean DBP (mm Hg) at follow-up	83.5 (80.0–88.0)	82.5 (80.0–90.0)	.73
Mean BP at target	82 (70.7)	18 (50.0)	.02
Maternal end-organ dysfunction at admission	14 (12.0)	5 (13.9)	.77
Progression toward severe hypertension before delivery	7 (6.0)	7 (19.4)	.02
Maternal end-organ dysfunction of new onset before delivery	13/102 (12.7)	3/31 (9.6)	.65
Need of a second-line therapy within 48–72 h	10 (8.6)	4 (11.1)	.65
Need of a second-line therapy before delivery	23 (19.8)	9 (25.0)	.51

Data are presented as median (interquartile range) or number (percentage), unless otherwise indicated.

BP, blood pressure; *DBP*, diastolic blood pressure; *SBP*, systolic blood pressure.

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a vasodilator (which decreases the peripheral vascular tone) is to be considered the most appropriate first-line antihypertensive agent to normalize the BP and to counteract the primary hemodynamic imbalance that poses that woman at risk of adverse events.[27,28]

In contrast, when the occurrence of hypertension in pregnancy is associated with a hyperdynamic profile of the mother (normal or higher CO and lower SVR), a negative inotrope and chronotrope drug (which decreases the CO) is to be considered the most appropriate first-line antihypertensive agent to normalize the BP and to counteract the primary hemodynamic imbalance that poses that woman at risk of adverse events.

In a smaller study conducted on 52 women presenting with untreated HDPs, the authors found that guiding the treatment of hypertension on the basis of maternal hemodynamic data obtained using noninvasive cardiac output monitoring (NICOM) reduced the incidence of severe hypertension compared with giving labetalol as a first-line agent independently from the maternal hemodynamic profile (from 18.0% to 3.8%).[23]

In a subsequent study on a cohort of 134 women, Stott et al[33] reported that 23% of women with HPDs treated with oral labetalol as a first-line therapy according to the National Institute for Health and Care Excellence guidelines required additional vasodilatory therapy. These unresponsive women had higher rates of severe hypertension (33.3% vs 2.9%; $P<.001$) and delivered smaller neonates at earlier gestational ages (2308 vs 3099 g [$P<.001$] and 39.0 vs 36.0 weeks [$P<.001$], respectively). All the study participants had been submitted to NICOM assessment of their hemodynamic profile before the start of antihypertensive therapy, and the unresponsive women were more likely to be hemodynamically unsuitable to beta-blockers because of higher SVR and lower heart rate and CO at presentation.

Here, 75% of the included women exhibited a hypodynamic cardiac profile featured by higher SVR and lower CO at presentation. Among this group, the use of a vasodilator (such as nifedipine or alpha methyldopa) as a first-line agent, which decreases the SVR, is to be considered hemodynamically appropriate. Moreover, a first-line agent was administered in most women (86%). In contrast, in the 25% of women who presented a hyperdynamic profile, less than half received a beta-blocker as a first-line agent, which is to be considered hemodynamically appropriate for this group. As nifedipine is the most commonly used antihypertensive agent in Italy, it is not surprising that most of the patients enrolled in our study were treated with nifedipine as a first-line agent, and this choice turned out to be the hemodynamically appropriate therapy for most patients who were found to present a hypodynamic profile.

Independently from the type of antihypertensive agent that was given as first-line treatment, if this was hemodynamically appropriate for the patient (vasodilator for hypodynamic profile and negative inotrope and chronotrope agent for the hyperdynamic profile), the occurrence of severe hypertension after admission and before delivery was less likely. Furthermore, the prompt treatment with a hemodynamically appropriate antihypertensive agent allowed to achieve more frequently a target BP at 48 to 72 hours from the treatment start compared with the cases who were inappropriately treated.

No significant difference in BP values was found between women who

received a hemodynamically appropriate treatment and women who received an inappropriate treatment.

Moreover, the need for a second-line therapy did not vary following the hemodynamic appropriateness of the antihypertensive treatment.

This may be due to the relatively small size of the study, which was not powered to find differences in the crude values of the BP based on the appropriateness of the treatment.

More importantly, rather than by lowering the absolute values of systolic, diastolic, or mean arterial pressure, the clinical benefit of a hemodynamically appropriate treatment seems to be witnessed by the ability to reduce the occurrence of severe hypertension and to keep the maternal BP in the optimal range, which were both demonstrated to be associated with the administration of a hemodynamically appropriate therapy.

As previously mentioned, 3 of 4 pregnant women with hypertension in our study demonstrated a hypodynamic phenotype. In this subgroup, compared with the hyperdynamic group, a higher incidence of SGA neonates and a lower gestational age at birth were noted, and this happened even when a hemodynamically appropriate therapy was initiated since admission. This is to be related to the hemodynamic features of this group at presentation as lower CO and higher SVR are known to be associated with FGR and more unfavorable perinatal outcomes.[34–39]

Clinical and research implications

Despite major advances in the pharmacologic treatment of hypertension in the nonpregnant population, the treatment of hypertension in pregnancy has remained largely unchanged over the years.[9–14] A subanalysis of a previous randomized controlled trial (Control of Hypertension In Pregnancy Study trial)[40] conducted on a population of women affected by HDPs failed to demonstrate any difference in the effectiveness of a specific pharmacologic agent against another in reducing the rate of severe complications in pregnancy. Here, it has to be noted that the first-line antihypertensive agent was prescribed without taking into account the patient's hemodynamic profile.

Our study confirmed the hypothesis that hypertensive disorders may derive from 2 different and opposite types of maternal cardiac imbalance.[16–23] The a priori knowledge of the associated hemodynamic phenotype could provide a potential opportunity for a targeted antihypertensive therapy that seeks to compensate for the underlying maternal cardiovascular disorder. Based on our results and other recent evidences, we envisage that an evaluation of maternal cardiovascular function in women with HDPs could help clinicians in improving maternal outcomes by lowering the occurrence of severe maternal complications.[23]

Mulder et al[41] recently found that, among pregnant women at risk of preeclampsia, the administration of antihypertensive agents tailored to the hemodynamic profile of the patient and administered in a preclinic phase of the disease is able to halve the risk of recurrent preeclampsia without disadvantageous effects on offspring outcomes.

Distinguishing among women with HDPs between "high-resistance" hypertension and "high-volume" hypertension and choosing the antihypertensive agent to be given on the basis of the hemodynamic profile challenge the general guidelines recommending a "one-for-all" pharmacologic treatment.[9–13]

It is plausible to speculate that a hemodynamically appropriate therapy of HDPs may also improve the long-term maternal outcome. To date, available data on the follow-up of women affected by HPD have demonstrated an increased risk of lifelong cardiovascular morbidity and mortality in women who experienced preeclampsia.[42,43]

Further studies are needed to clarify whether a hemodynamically appropriate treatment of de novo hypertension in pregnancy may also be associated with improved echocardiographic findings during the early postpartum period and with an improved maternal outcome in long-term follow-up.

Strengths and limitations

The prospective, original, and multicentric design may be acknowledged as one of the main strengths of our study. Furthermore, we included only women with new-onset HDPs who were naïve to any type of antihypertensive treatment.

Among the main limitations, a selection bias has to be acknowledged as a higher percentage of included women had a hypodynamic pattern in our sample. It has been previously reported that this hemodynamic pattern is associated with FGR together with an earlier gestational age at onset and with a more severe clinical presentation. Thus, these women are more frequently referred to the tertiary care units than women presenting with the opposite hemodynamic pattern (higher CO or low resistance) who usually carry normal-sized or large fetuses and have a later or less severe clinical presentation.

The use of USCOM 1-A for the hemodynamic assessment of pregnant patients has been demonstrated to have excellent inter- and intraobserver reproducibility if performed by a trained operator.[44] Therefore, the recruitment of the women was based on the availability of an operator with dedicated skills in the use of this device. This represents not only as a strength but also as a limitation of the study because the patient's enrollment was not consecutive.

Lastly, data regarding the neonatal follow-up (eg, length of hospitalization or neonatal intensive care unit admission) were not collected, as this study was primarily interested in maternal outcome.

Conclusion

Our study shows that a less frequent progression toward severe hypertension and a tighter BP control are achieved in pregnant individuals with de novo HDPs when the first-line antihypertensive agent is tailored to the correct maternal hemodynamic profile. Further studies are needed to validate our findings and to assess the potential benefits of a hemodynamically tailored antihypertensive therapy on the long-term outcomes of the affected women. ■

CRediT authorship contribution statement

Elvira di Pasquo: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Stefano Raffaele Giannubilo:** Writing – review & editing, Data curation. **Beatrice Valentini:** Data curation. **Silvia Salvi:** Writing – original draft, Conceptualization. **Roberta Rullo:** Data curation. **Stefano Fruci:** Data curation. **Elisa Filippi:** Writing – original draft, Data curation. **Sara Ornaghi:** Writing – original draft, Data curation. **Sara Zullino:** Data curation, Writing – original draft. **Francesca Rossi:** Data curation. **Daniele Farsetti:** Formal analysis, Writing – original draft, Data curation. **Daniela Denis Di Martino:** Writing – original draft, Data curation. **Barbara Vasapollo:** Writing – review & editing, Conceptualization. **Anna Locatelli:** Writing – review & editing, Supervision. **Michela De Santis:** Data curation. **Andrea Ciavattini:** Writing – review & editing. **Antonio Lanzone:** Writing – review & editing. **Federico Mecacci:** Supervision, Data curation, Writing – review & editing. **Enrico Ferrazzi:** Supervision, Conceptualization. **Hebert Valensise:** Writing – review & editing, Supervision, Conceptualization. **Tullio Ghi:** Conceptualization, Supervision, Writing – review & editing. ■

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajogmf.2024.101368.

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Author and article information

From the Department of Obstetrics and Gynecology, University Hospital of Parma, Parma, Italy (Drs di Pasquo, Valentini, and Ghi); Department of Clinical Sciences, Università Politecnica delle Marche, Ancona, Italy (Drs Giannubilo and Ciavattini); High-Risk Pregnancy Unit, Dipartimento Scienze della Salute della Donna, del Bambino e di Sanità Pubblica, Fondazione Policlinico Universitario A. Gemelli Istituto di Ricovero e Cura a Carattere Scientifico, Largo Agostino Gemelli, Rome, Italy (Drs Salvi, Rullo, Fruci, and Lanzone); Department of Obstetrics and Gynecology, Ospedale Ca Foncello, Treviso, Italy (Drs Filippi and Santis); Department of Obstetrics, University of Milan-Bicocca, Foundation Istituto di Ricovero e Cura a Carattere Scientifico San Gerardo dei Tintori, Milan, Italy (Drs Ornaghi, Rossi, and Locatelli); High-Risk Pregnancy Unit, Department of Women's and Children's Health, Azienda Ospedaliera Careggi, Florence, Italy (Drs Zullino and Dr Mecacci); Division of Obstetrics and Gynecology, Department of Surgical Sciences, Policlinico Casilino, Tor Vergata University of Rome, Rome, Italy (Drs Farsetti, Vasapollo, and Valensise); Unit of Obstetrics, Division of Obstetrics and Gynecology, Department of Woman, Child, and Newborn, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy (Drs Di Martino and Ferrazzi); Obstetrics and Gynaecology Unit, Department of Medicine and Surgery, University of Parma, Parma, Italy (Dr Ghi).

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Corresponding author: Tullio Ghi, PhD. tullioghi@yahoo.com