Hypertension

ORIGINAL ARTICLE

First-Trimester Normotension Is a Weak Indicator of Normal Maternal Cardiovascular Function

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BACKGROUND: As by definition, mean arterial pressure equals the product of cardiac output (CO) and total vascular resistance (TPR), we hypothesized that, irrespective of thresholds to define hypertension, a CO-TPR imbalance might exist in first-trimester normotensive pregnancies with altered risks for adverse gestational outcomes.

METHODS: A standard protocol was used for automated blood pressure measurement combined with impedance cardiography assessment of CO and TPR (NICCOMO). First-trimester normotensive pregnant women were categorized into 3 groups relative to the reference 75th percentile (P75) of CO and TPR: (1) normal CO and TPR, (2) high CO, and (3) high TPR. These subgroups were compared at blood pressure thresholds 140/90, 130/85, and 130/80 mmHg. The gestational outcome was categorized after birth according to International Society for Studies of Hypertension in Pregnancy criteria.

RESULTS: Compared with pregnancies with normal CO and TPR (≤P75), women with high TPR at blood pressure <140/90 mmHg are at risk for developing gestational hypertension (odds ratio, 3.795 [1.321–10.904]; $P<0.010$), late-onset preeclampsia (odds ratio, 3.137 [1.060–9.287]; $P<0.050$), and neonates small for gestational age (odds ratio, 1.780 [1.056–2.998]; $P<0.050$).

CONCLUSIONS: Cardiovascular imbalance can present in normotensive women in the first trimester and is associated with increased risks for adverse gestational outcomes. This study illustrates the relevance of CO and TPR assessments as an adjunct to blood pressure measurement and invites for further exploring their value in screening algorithms for gestational hypertensive disorders and/or small for gestational age. **(*Hypertension*. 2023;80:343–351. DOI: 10.1161/HYPERTENSIONAHA.122.19346.)** • **Supplemental Material**

Key Words: blood pressure ■ cardiac output ■ cardiovascular function ■ gestational hypertensive disorders ■ total peripheral resistance

Definitions of gestational hypertensive disorders (GHDs), set by international societies of Obstetricians & Gynecologists such as the American College of Obstetricians and Gynecologists (ACOG) and the International Society for Studies of Hypertension in Pregnancy (ISSHP) share 140/90 mmHg as the common blood pressure (BP) threshold to discriminate hypertension from normotension.[1,2] Since 2017, societies of cardiovascular physicians agreed to lower this BP threshold to 130/85 or 130/80 mmHg, as defined by the World Health Organization and the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, respectively.[3,4] This new cutoff is not commonly practiced in perinatal care yet. Nevertheless, it has already been reported that women destined to develop gestational hypertension (GH), preeclampsia, and/or fetal growth restriction show higher BPs in the first trimester than women with normal gestational outcome.[5–7] BP relates to the balance between intravascular blood flow and vascular wall resistance according to the hemodynamics variant of Ohm's law:

Mean arterial pressure (MAP)=cardiac output (CO)x total peripheral resistance (TPR).[8]

Hence, hypertension can result from high CO at one end, high TPR at the other end, and a spectrum of

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ORIGINAL ARTICLE

NOVELTY AND RELEVANCE

What Is New?

Normotension presents with a spectrum of cardiovascular conditions ranging between volume-dominant to resistance-dominant circulations.
In early pregnancy, normotension does not necessarily indicate normal gestational complication risk.

What Is Relevant?

A more in-depth evaluation of the true nature of an individual's blood pressure by measuring its determinants cardiac output and peripheral vascular resistance allows for better estimating the overall cardiovascular health condition than conventional, standardized blood pressure measurement.

Clinical/Pathophysiological Implications?

It is to be determined whether certain cardiovascular risk profiles already require early intervention for prevention of cardiovascular disease, even when blood pressure is still normal.

Nonstandard Abbreviations and Acronyms

BP	blood pressure
CO	cardiac output
EPE	early-onset preeclampsia
GH	gestational hypertension
GHD	gestational hypertensive disorders
LPE	late-onset preeclampsia
P75	75% cut-off of the first-trimester reference ranges
SGA	small for gestational age
TPR	total peripheral resistance

combinations in between. This bimodal nature of hypertension has also been reported for GH and preeclampsia.[9]

For this study, we hypothesized that a subclinical imbalance between CO and TPR might be present in women with normotension in the first trimester of pregnancy, irrespective of the BP threshold used to define hypertension, implicating altered risk for GHD.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

Women with singleton pregnancies attending the obstetric ultrasound scanning clinic for routine obstetric scan at Ziekenhuis Oost-Limburg (ZOL, Genk, Belgium), as well as pregnant women referred to the Maternal-Fetal-Medicine Department of the same hospital with suspected new-onset hypertension in ambulatory or hospital setting, were invited to participate in a prospective, observational study on maternal cardiovascular functioning between 2011 and 2017, as part of the ongoing Hasselt University Research Project of Maternal Venous Hemodynamics. Approval of the institutional review board "Medical Ethical Committee of ZOL" was obtained before study onset, and participants provided written informed consent before inclusion (Medical ethical committee reference: 06/043, 08/049, 13/090U). At birth, the gestational outcome was defined and categorized according to ISSHP into uncomplicated pregnancies with the birth of neonates appropriate or large for gestational age, normotensive pregnancies complicated with the birth of neonates small for gestational age (SGA), or pregnancies complicated with GHD. The latter included GH or preeclampsia de novo or superimposed on chronic hypertension. GH was defined as new-onset hypertension (systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg) observed at gestation >20 weeks, measured twice with 6 hours in between, without proteinuria or maternal organ dysfunction. The diagnosis of preeclampsia was determined when GH was accompanied by de novo proteinuria (≥300 mg per 24 hours), other maternal organ dysfunctions, and/or fetal growth restriction. Preeclampsia was subsequently subdivided into early-onset preeclampsia (EPE) or late-onset preeclampsia (LPE) requiring delivery before or at/after the 34th week of gestation, respectively.[2] According to a customized birth weight chart, SGA was defined as neonatal birth weight <percentile 10.[10] Multiple pregnancies, women on antihypertensive medication at inclusion, and women with essential hypertension, pre-existing cardiac, renal, endocrine, hematologic, or autoimmune diseases were excluded.

The following demographic and clinical characteristics were recorded: maternal age (years), pregestational body mass index, gestational age at assessment and delivery, parity, smoking, medication, neonatal birth weight, and percentile. The procedures followed were in accordance with institutional guidelines.

Cardiovascular Assessment

Systolic BP, diastolic BP, MAP, CO, and TPR were assessed through impedance cardiography using the Non-Invasive Continuous Cardiac Output Monitor (NICCOMO©, Medis Medizinische Messtechnik GmbH, Ilmenau, Germany) as part of a reported standardized non-invasive cardiovascular assessment protocol at first trimester (gestational age <15 weeks).[11] Automated BP measurements were taken on the right arm with an appropriate cuff width in supine and after 2 minutes in a standing position using an oscillometric sphygmomanometer according to a standard protocol (Figure 1). For this analysis, we only used measurements in standing position, as they show better prediction for GHD than those in sitting position.[12]

Standardized measurement of CO and TPR was performed using 4 skin resistance-eliminating electrodes: 2 on the axillary line under the thorax and 2 in the neck. Impedance cardiography was performed for 3 min after stabilizing cardiovascular function in the standing position (Figure 1). Cardiac function parameters are heart rate in beats per minute and stroke volume in milliliters, as calculated from the impedance cardiography measurements using the formula of Bernstein and Lemmens.[13] CO in liters per minute is calculated as heart rate×stroke volume, and TPR is calculated as MAP×80/CO expressed in dyn·s·cm^{-5}.[14] Other cardiovascular parameters were recorded and registered but are not discussed in this article.

The NICCOMO measurements were compared with population-and-technology-specific reference ranges.[15,16] The normal reference ranges are based on 910 first-trimester cardiovascular measurements performed in uncomplicated pregnancies. The uncomplicated pregnancies-reference values have been reported as least squares means of age-, parity-, and body mass index-corrected values together with interquartile range of raw data. Mean values were estimated for a 30-year-old primigravid subject with body mass index of 23 kg/m^2. The first-trimester reference ranges for CO and TPR (mean [IQR]) are 7 (6.3–7.9) L/min and 993 (85–1084) dyn·s·cm^{-5}, respectively.[11]

Women were included in 1, 2, or 3 categories depending on the first-trimester BP value below the hypertension threshold set by ACOG/ISSHP at 140/90 mmHg, World Health Organization at 130/85 mmHg, and ACC/AHA at 130/80 mmHg. All women also had MAP ranging between 60 and 100 mmHg for both supine and standing position (Figure 2). For study-specific research purposes, each category was additionally subdivided into 3 cardiovascular profile groups depending on the CO and TPR results being either equal to or below the 75% cutoff (≤P75) or exceeding this threshold (>P75) of the first-trimester reference ranges: CO and TPR ≤P75 (group 1), CO >P75 and TPR ≤P75 (group 2), or CO ≤P75, and TPR >P75 (group 3).[11]

Statistics

Statistical analysis was performed with Statistical Package for Social Sciences release 28.0 (IBM SPSS Statistics, Chicago, IL). Normality was checked via Shapiro-Wilk for continuous variables. One-way ANOVA and Bonferroni post-hoc testing or Independent-Samples Kruskal-Wallis Test were used for continuous demographic data intergroup comparison, depending on normality. The χ^2 test and/or Fisher Exact test were used for categorical demographic variables. The Haldane-Anscombe correction was used for odds ratio calculations in case of 0 cell counts. Data are presented as mean±SD, number (n), and percentage (%), or median and interquartile range (IQR). All analyses were done at a 5% significance level. PD had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

RESULTS

Number of Inclusions

A total of 1109 first-trimester measurements were registered in the database of the Hasselt University Research Project of Maternal Venous Hemodynamics between 2011 and 2017. Of these, 961 women had BP<140/90 mmHg, 813 had BP<130/85 mmHg, and 661 women had BP<130/80 mmHg for both supine and standing position (Figure 2). For these populations, the distribution of the 3 cardiovascular profiles—(1) normal CO and TPR, (2) high CO, and (3) high TPR relative to the 75th percentile (P75) of normal reference ranges—is shown in Figure 3.

Demographics

No race/ethnicity-based differences were present. The demographics and maternal and neonatal outcomes of pregnant women with a first-trimester BP <140/90 mmHg (ACOG/ISSHP) are compared between the 3 CO-TPR groups: CO and TPR ≤P75 (group 1), CO >P75 and TPR ≤P75 (group 2), and CO ≤P75 and TPR > P75 (group 3; Table 1). Group 2 (high CO) had a lower mean maternal age, a higher pre-pregnancy body mass index, and assessments slightly later in first trimester compared with the other groups. Furthermore, they also had neonates with a higher mean birth weight and birth weight percentile. The percentage of women with a history of hypertensive gestation was higher for group 3 (high TPR) compared with group 1 (normal CO and TPR). Other maternal and neonatal characteristics did not differ between groups. Similar intergroup comparisons at BP <130/85 and/or <130/80 mmHg are shown in Tables S1 and S2, respectively.

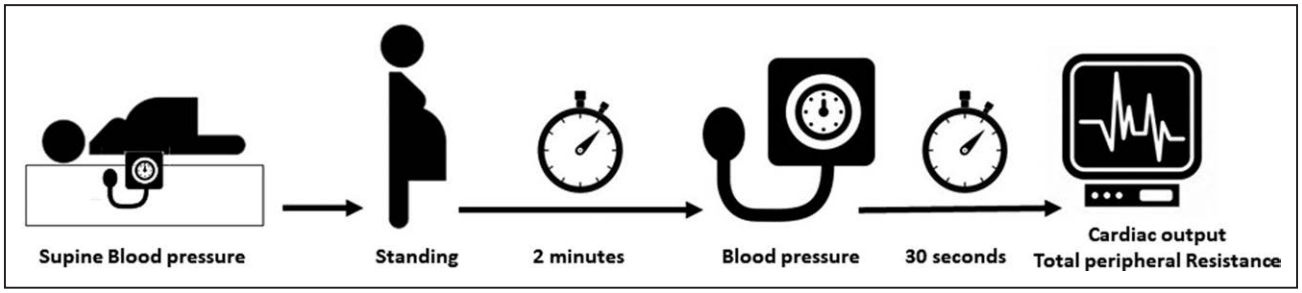

Figure 1. First-trimester supine and standing blood pressure, cardiac output, and total peripheral resistance measurement as part of the non-invasive continuous cardiac output monitor (NICCOMO) assessment, according to a standardized protocol.[11,12]

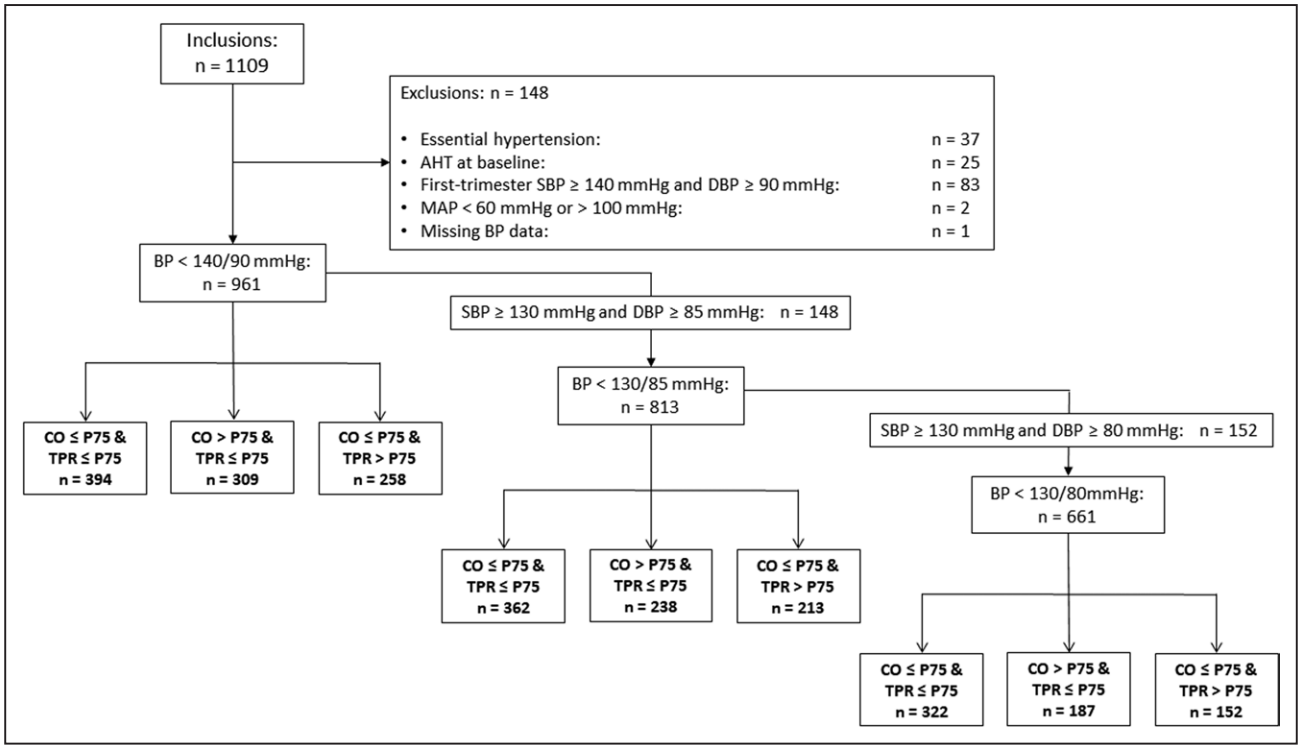

Figure 2. Flowchart of first-trimester normotensive pregnancies relative to 3 different blood pressure (BP) thresholds set by ACOG/ISSHP at 140/90 mmHg, WHO at 130/85 mmHg, and ACC/AHA at 130/80 mmHg.[3,4,2]
All women included were categorized in one of 3 groups according to the cardiovascular profile: normal cardiac output (CO) and total peripheral resistance (TPR), high CO, or high TPR relative to the 75th percentile of normal reference ranges.[11]

Pregnancy Outcome

Gestational outcome was not different between group 1 (normal CO and TPR) and group 2 (high CO). However, group 3 (high TPR) had significantly more pregnancies complicated with GHD and SGA compared with the other groups. The distribution of GHD subtypes (EPE, LPE, and GH) did not differ between the groups (Table 1). Group-specific gestational outcomes in women with first-trimester normotension relative to other BP thresholds are shown in Tables S1 and S2.

Gestational Complications at Different BP Thresholds

The combined rate of GHD and SGA in the 3 cardiovascular profile groups at different BP thresholds is presented in Figure 4. Around 10% of normotensive women with a first-trimester normal CO and TPR eventually developed GHD and/or SGA, irrespective of the BP threshold (Group 1, depicted in blue). As compared with group 1, there was a trend for more gestational complications in women with a high CO (Group 2, depicted in orange), although this difference was not significant. On the other hand, group 3 consisting of women with a high TPR (depicted in grey) showed higher complication rates than the other groups.

Risk Estimates for GHD and SGA

The odds ratios and 95% CIs for developing GH, LPE, EPE or SGA in normotensive pregnant women with a first-trimester high CO (Group 2) or a high TPR (Group 3) against reference group 1 (normal CO and TPR) have been calculated at different BP thresholds and are shown in Table 2 and Figure S1. Women with a high TPR at BP <140/90 mmHg are at increased risk for developing GH (odds ratio, 3.795 [1.321–10.904]; $P<0.010$), LPE (odds ratio, 3.137 [1.060–9.287]; $P<0.050$), and SGA (odds ratio, 1.780 [1.056–2.998]; $P<0.050$; Table 2). Even below a stricter BP threshold of 130/85 mmHg, these increased risks hold for GH and SGA, and at BP<130/80 mmHg still for SGA.

DISCUSSION

The main finding of this study is that normotension can present with a variety of measured values of CO and TPR, ranging from high to low, representing circulatory functioning in volume-dominant or resistance-dominant conditions. This physiological spectrum is independent of the criteria used to define hypertension. In the first trimester of pregnancy, (1) less than half of normotensive women have a combination of both normal to low CO and TPR (<normal reference 75th percentile) and (2) particularly the normotensive women with high

Table 1. Demographics and Maternal and Neonatal Outcomes of Women With First-Trimester Pregnancy Normotension Defined as Systolic Blood Pressure <140 mmHg and Diastolic Blood Pressure <90 mmHg (ACOG/ISSHP)

	CO≤P75 and TPR≤P75	CO>P75 and TPR≤P75	CO≤P75 and TPR>P75	*P* value (G1 vs G2)	*P* value (G1 vs G3)	*P* value (G2 vs G3)	*P* value between groups
	Group 1 (G1)	Group 2 (G2)	Group 3 (G3)				
No. of assessments (% total)	394 (41.00%)	309 (32.15%)	258 (26.85%)	/	/	/	/
Demographics							
Age, y	30.76±4.50	29.51±4.62	31.35±4.58	*P*<0.001	NS	*P*<0.001	*P*<0.001
GA at assessment, wks	12.18±0.74	12.34±0.77	12.16±0.77	*P*<0.050	NS	*P*<0.050	*P*<0.010
Prepregnancy BMI, kg/m²	23.25±3.26	27.03±5.14*	22.06±3.71†	*P*<0.001	*P*<0.001	*P*<0.001	*P*<0.001
Nulliparity, n (% women)	181 (45.94%)	149 (48.22%)	132 (51.16%)	/	/	/	NS
Cigarette smoker, n (% women)				/	/	/	NS
Active	53 (16.41%)‡	35 (14.77%)§	31 (14.22%)‖				
Former	17 (5.26%)‡	15 (6.33%)§	8 (3.67%)‖				
History of diabetes, n (% women)	50 (12.69%)	34 (11.00%)	38 (14.73%)	/	/	/	NS
History of thrombophilia, n (% women)	13 (3.30%)	11 (3.56%)	12 (4.65%)	/	/	/	NS
History of hypertension in previous pregnancy, n (% women)	15 (3.81%)	20 (6.47%)	23 (8.91%)	NS	*P*<0.010	NS	*P*<0.05
Familial hypertension, n (% women)	13 (3.30%)	16 (5.18%)	10 (3.88%)	/	/	/	NS
Medication, n (% assessments)				/	/	/	NS
Anticoagulantia	17 (4.31%)	14 (4.53%)	19 (7.36%)				
Other	43 (10.91%)	31 (10.03%)	26 (10.08%)				
Outcome characteristics							
GA at delivery, wks	39.72 (IQR 1.56)	39.86 (IQR 2.00)	39.57 (IQR 1.71)	/	/	/	NS
Birth weight, g	3326.49±514.55	3431.40±589.62	3210.49±520.88¶	*P*<0.050	*P*<0.050	*P*<0.001	*P*<0.001
Birth weight percentile, %	50.60±28.06	56.30±28.94	43.21±27.18¶	*P*<0.050	*P*<0.010	*P*<0.001	*P*<0.001
Pregnancy outcome							
UP	353 (89.59%)	268 (86.73%)	202 (78.29%)	NS	*P*<0.001	*P*<0.050	*P*<0.001
SGA	30 (7.61%)	23 (7.44%)	33 (12.79%)				
GHD	11 (2.79%)	18 (5.83%)	23 (8.91%)				
EPE	1 (9.09%)	3 (16.67%)	1 (4.35%)	/	/	/	NS
LPE	5 (45.45%)	9 (50.00%)	10 (43.48%)				
GH	5 (45.45%)	6 (33.33%)	12 (52.17%)				

ACOG indicates American College of Obstetricians and Gynecologists; CO, cardiac output; EPE, early-onset preeclampsia; GA, gestational age; GH, gestational hypertension; GHD, gestational hypertensive disorder; IQR, interquartile range; ISSHP, International Society for Studies of Hypertension in Pregnancy; LPE, late-onset preeclampsia; n, number of subjects; SGA, pregnancies complicated with the birth of neonates small for gestational age; TPR, total peripheral resistance; and UP, uncomplicated pregnancy.

*3 missing values (n=306).
†2 missing values (n=256).
‡71 missing values (n=323).
§72 missing values (n=237).
‖40 missing values (n=218).
¶1 missing value (n=257).

first-trimester TPR are at increased risk for development of GHD and/or SGA.

The strengths of this study are that a large population was screened according to a stringent protocol, with subsequent longitudinal follow-up and well-documented perinatal outcome data. Our methodology allows obtaining BP measurements in both standing and sitting position. As we reported elsewhere, first trimester values in standing position show better predictive performance for GHD than those in sitting position.[12] In addition to this, the impedance cardiography measurement (NICCOMO) also allows evaluating the orthostatic hemodynamic response after posture change between supine and active standing, which has shown to be different in preeclamptic pregnancies compared with uncomplicated pregnancies.[17]

Next to this, normal reference values for a large set of maternal cardiovascular function parameters are available from a population of ≈ 1000 women with confirmed normal outcomes.[11] A weakness is that the registration of gestational complications is focused on hypertension and fetal growth, excluding other complications from analysis, such as premature births, abruptions, or others. Another point of discussion might be using the predefined cut-off point "P75" to discriminate

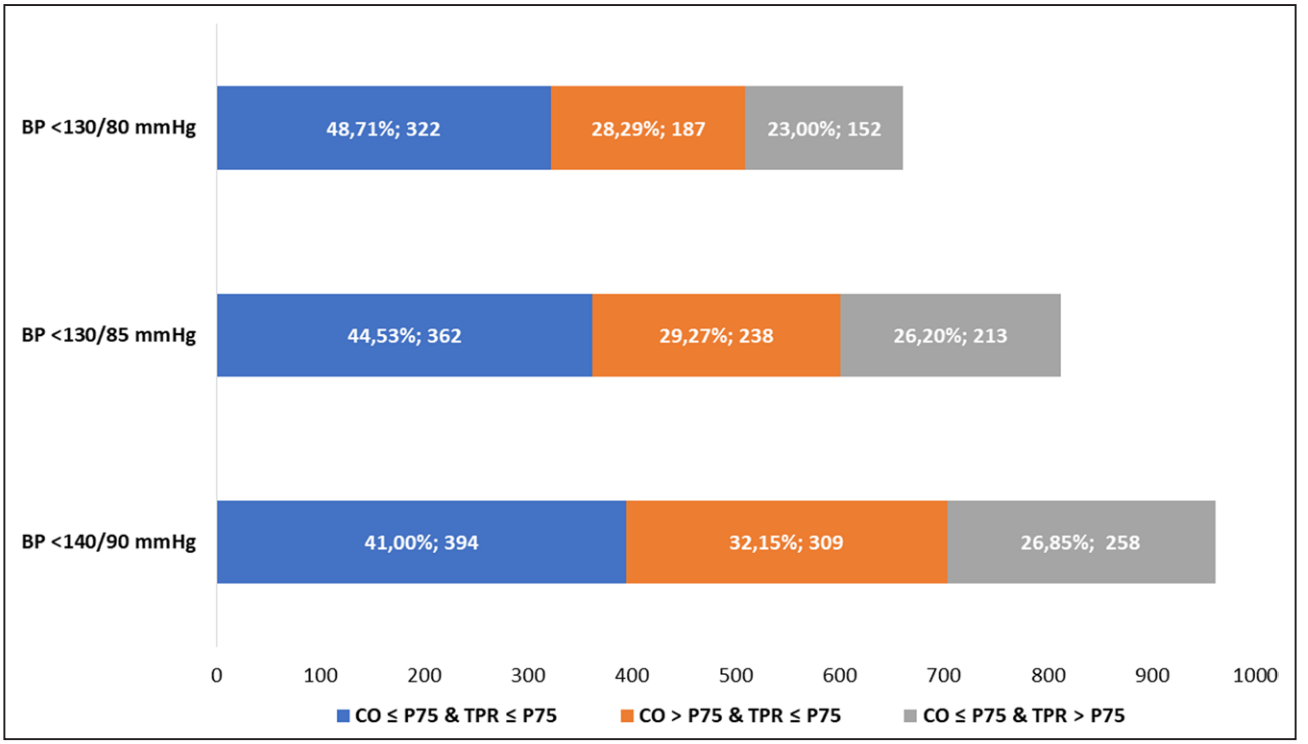

Figure 3. Distribution of 3 first-trimester cardiovascular profiles in normotensive women: normal cardiac output (CO) and total peripheral resistance (TPR; blue), high CO (orange), and high TPR (gray) relative to the 75th percentile of normal reference ranges (P75).[11]

Fractions are presented for 3 different blood pressure (BP) thresholds: <130/80 mmHg (upper), <130/85 mmHg (middle), and <140/90 mmHg (lower panel). The *x*-axis represents the cumulative number of women, group specific records are presented as % (n).

normal from abnormal cardiovascular function measurements, as other threshold values have not been evaluated.

For many decades now, maternal BP measurement has been one of the most important clinical assessments in prenatal care, and the recorded values are universally used

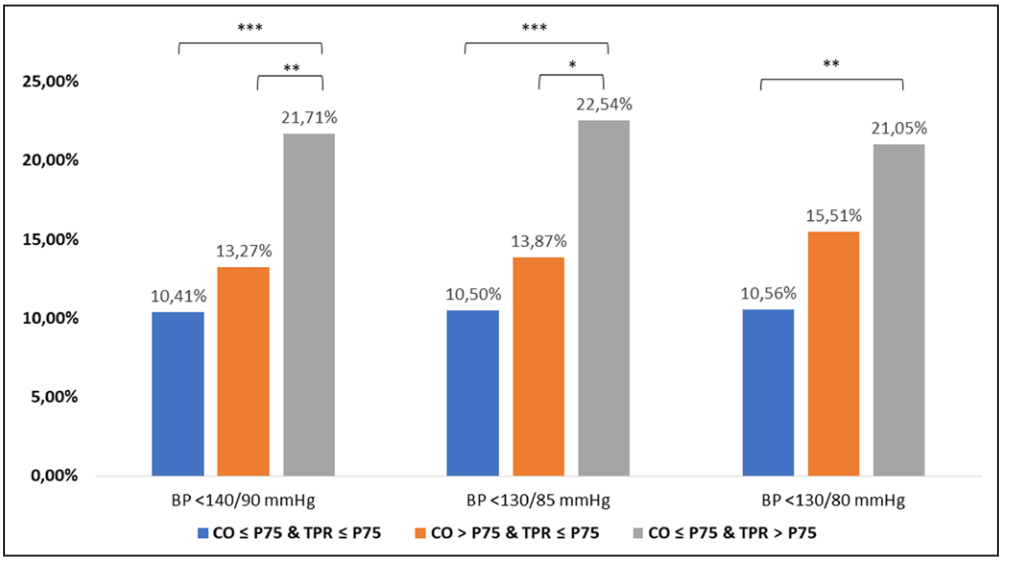

Figure 4. Comparison of the percentage of gestational complication rate (gestational hypertensive disorders and/or birth of neonates small for gestational age) between the groups with first-trimester normal cardiac output (CO) and total peripheral resistance (TPR; blue), high CO (orange), and high TPR (gray) relative to the 75th percentile of normal reference ranges (P75).[11]

Data are presented for 3 different blood pressure (BP) thresholds: <140/90 mmHg (left), <130/85 mmHg (middle), and <130/80 mmHg (right). *, **, and *** indicate significance level $P<0.05$, $P<0.010$, and $P<0.001$ respectively.

Table 2. Odds Ratio Against Reference Group 1 and (95% CI) for Developing GH, LPE, EPE, or Neonates SGA at Different BP Thresholds for Normotensive Pregnant Women With a High First-Trimester CO>P75 or a High First-Trimester TPR>P75

		BP<140/90 mmHg)	BP<130/85 mmHg)	BP<130/80 mmHg)
CO>P75	*GH*	1.541 (0.466–5.096)	1.221 (0.324–4.592)	1.738 (0.429–7.031)
	LPE	2.334 (0.774–7.037)	2.164 (0.679–6.898)	2.635 (0.734–9.462)
	EPE	3.853 (0.399–37.223)	4.609 (0.477–44.569)	7.000 (0.777–63.098)
	SGA	0.976 (0.555–1.717)	1.076 (0.584–1.983)	1.065 (0.556–2.042)
TPR>P75	*GH*	3.795 (1.321–10.904)†	3.517 (1.186–10.433)*	3.267 (0.908–11.753)
	LPE	3.137 (1.060–9.287)*	1.716 (0.491–5.999)	1.060 (0.192–5.852)
	EPE	1.529 (0.095–24.557)	1.703 (0.106–27.365)	2.118 (0.132–34.096)
	SGA	1.780 (1.056–2.998)*	2.194 (1.274–3.776)†	2.135 (1.181–3.860)*

BP indicates blood pressure; CO, cardiac output; EPE, early-onset preeclampsia; GH, gestational hypertension; LPE, late-onset preeclampsia; SGA, small for gestational age; and TPR, total peripheral resistance.

*P<0.050.

†P<0.010.

for screening, diagnosis, and management of GHD. Our data clearly show that this parameter can be associated with a variety of measured values of CO and TPR, ranging from low to high, even in women with normotension. According to Ohm's law, defining MAP as the product of CO and TPR, abnormally high or low values of one determinant can be outbalanced by an opposite trend of the other one, with normotension as the clinical end result. As shown in Figure 3, the latter situation is even true for the majority of women. This clearly indicates that the diagnosis of normotension does not represent a normal cardiovascular function in at least half of our study population. Our analysis also shows that this finding is independent from the definitions used to define normo- and hypertension.

The clinical relevance of this observation is reflected in increased odds ratios for GHD and/or SGA in first-trimester normotensive women with high TPR (Table 2). For women with high CO, the odds for the development of hypertension during the course of pregnancy are borderline increased relative to women with normal cardiovascular assessment (Table 2). Our results indicate that first-trimester normotensive women have a different risk profile for development of gestational complications, depending on the balance between CO and TPR. This finding supports the relevance of introducing simple, non-invasive technologies to perform basic maternal cardiovascular function assessments in routine and high-risk prenatal care for improved discrimination between true and false normotension with associated normal or abnormal risk profiles, respectively.[18] From this, it seems likely that the replacement of MAP by its determinants "CO" and "TPR" is beneficial to the performance of current first-trimester screening algorithms for preeclampsia and/or fetal growth restriction.[19] However, this warrants further assessment.

Another important finding of our study is that 10% of women with confirmed normal first-trimester values of CO and TPR gave birth to a neonate SGA, but more importantly: 2% to 3% developed GH, LPE or even EPE (Table 1). This finding adds to the current debate on the origins of preeclampsia, which for long has been considered to result from an abnormal placentation process associated with shallow dilatation of spiral arteries,[20] a theory recently challenged by observations of pre-existing subclinical maternal cardiovascular dysfunction prior to conception.[21,22] Our data support both theories, indicating once more that preeclampsia is a multifaceted disorder with multiple predisposing factors followed by a cascade of pathophysiologic events.[22]

Clinical Implications

Our data implicate that, next to the use of standardized and validated methods to measure BP, it is also important to measure its determinants "CO" and "TPR" to understand the background mechanisms of the measured BP value and to estimate better an individualized risk profile for development of gestational complications.[23]

MAP is an important parameter for implementation in most current screening algorithms for preeclampsia and/or poor fetal growth.[19]

Our data show that normal BP can present with abnormal CO or TPR. Replacement of MAP by CO and TPR might likely change the calculated risk. Our findings are consistent and independent from the definitions used to define hypertension.

Perspectives

Our data shed a new light on the old and universally accepted concept in cardiovascular health: normotension as in indicator of normal cardiovascular health. Normotension represents a spectrum of cardiovascular conditions ranging from volume-dominant to resistance-dominant circulations which, using pregnancy as an example, reflect different risk profiles for cardiovascular complications. This finding is independent from the thresholds used to define hypertension. Whether the variable gestational risk profile is associated with long term cardiovascular health

or disease is to be explored further. Our findings are in support of more in-depth evaluation of the true nature of an individual's BP by measuring its determinants CO and TPR in addition to conventional, standardized BP measurement.

Conclusions

Our study supports the hypothesis that a physiological spectrum of CO and TPR levels ranging from high to low can present in first-trimester normotensive pregnant women and an imbalance can be associated with increased risk for development of GHD and SGA, irrespective of the hypertension threshold. Less than half of the normotensive women had a combination of both CO and TPR below the normal reference 75th percentile in the first trimester of pregnancy and 10% eventually developed GHD and/or SGA. Our results showed that a high TPR above the normal reference 75th percentile increases the risk for LPE, GH, and SGA.

Since normotension can mask a subclinical abnormal maternal cardiovascular function, perinatal care should include routine cardiovascular profiling to assess determinants of MAP, next to conventional BP measurements. The added value of these cardiovascular parameters in prenatal screening tools for GHD and/or SGA should be explored in future research. Our data also implicate that preeclampsia can develop in normotensive women with and without normal CO and/or TPR, supporting both the theories of placental and cardiovascular origins of preeclampsia.

ARTICLE INFORMATION

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Disclosures

None.

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