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Vascular and autonomic function as early predictive biomarkers of the progression to gestational hypertension

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ABSTRACT

Background: The changes in endothelial function, arterial stiffness, and heart rate variability (HRV) produced in the first trimester of pregnancy in women who develop gestational hypertension (GH) are still being investigated. Objective: to evaluate the HVR, endothelial function, and arterial stiffness changes during the first trimester of pregnancy and their relationship with the development of GH

Methods: A group of women normotensive during the first trimester (n = 43), who later did (GH; n = 11) or did not (no-GH; n = 32) develop GH in that pregnancy, were enrolled. In the first trimester, endothelial function and arterial stiffness were evaluated through photoplethysmography. HRV, parasympathetic (PNS), and sympathetic (SNS) indexes were measured in a 5-minute continuous electrocardiogram record at rest sitting. The Griess reaction measured urinary nitrite excretion (NOx).

Results: Systolic blood pressure (SBP) values were higher in GH (no-GH: 105.8 ± 2.0 vs. GH: 112.7 ± 3.0 mmHg; $p < 0.05$). Endothelial function was decreased, and arterial stiffness was increased in GH. Only in GH the arterial stiffness was correlated with SBP (Pearson's r: 0.5594; 95%CI: 0.06106–0.8681; $p < 0.05$). In HRV, GH decreased low-frequency power and the ratio SD2/SD1. The inhibition of PNS was lower in GH. The NOx was reduced in GH (no-GH: 3.4 ± 0.4 vs. GH: 0.3 ± 0.1 μM/L; $p < 0.001$). NOx was correlated negatively with the SNS index only in GH.

Conclusions: Developed GH is preceded early in pregnancy by endothelial dysfunction and increased arterial stiffness. In this context, there are SNS-PNS interrelation modifications with less inhibition of PNS.

1. Introduction

Gestational hypertension (GH) is defined as hypertension that appears de novo after 20 weeks of gestation and normalizes after pregnancy [1]. GH is associated with an increased risk of preterm birth [2] and perinatal mortality and predisposes to complications in future pregnancies, like GH, gestational diabetes, and obstetric cholestasis [3]. Classically, in GH, it is described that alterations in vascular reactivity are detected for 14 weeks of pregnancy [4]. These alterations included alterations in flow-mediated relaxation in the brachial artery without alterations in vascular structure [5] with an exaggerated sympathetic overdrive associated [6]. However, there are no premonitory studies in the first trimester of pregnancy.

Recently, we showed that, in healthy women, heart rate variability (HRV) decreased in the first trimester of pregnancy and that the newborn weight positively correlated with the parasympathetic (PNS) index. In this study, we observed that in PG, the PNS index was decreased, whereas the SNS index was increased, but the decrease in the PNS index (–45 ± 7%) was lower than the increase in the SNS index (+282 ± 120%; $p < .05$). Thus, we proposed that although the sympathetic (SNS) activation plays a compensatory hemodynamic role, the low rates of parasympathetic (PNS) inhibition are essential to ensure normal fetal growth [7]. Also, we observed that these adaptative changes were accompanied by an increase in the endothelial function and a decrease in arterial stiffness [7].

1.1. Specific aims of the study

Evaluate the HVR, endothelial function, and arterial stiffness changes during the first trimester of pregnancy and their relationship

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with the development of GH.

2. Material and methods

2.1. Design

The present is an analytical cross-sectional study.

2.2. Participants

In order to determine the possible alterations of vascular function in the early stages of pregnancy, a group of women during the first trimester (5–12 weeks of gestation) was enrolled in the Instituto de Maternidad Nuestra Señora de las Mercedes (Tucumán, Argentina).

Exclusion criteria: background of cardiovascular disease, hypertension, history of preeclampsia or glycemic disturbances in previous pregnancies, diabetes, glucose intolerance, and smoking. Also, in the current pregnancy, we have excluded patients who presented multiple pregnancies or clinical reports of infections. After delivery, each patient's medical history was evaluated, and patients that developed preeclampsia, eclampsia, or those who persisted with high blood pressure, were excluded.

Thus, the group was divided into two groups: those who did (GH; n = 11) or did not (no-GH; n = 32) develop GH.

2.3. Instruments and procedure

The following data were collected from each woman during the first trimester of pregnancy.

2.3.1 Hemodynamic variables

At the moment of the study, the systolic (SBP), diastolic (DBP), and heart rate (HR) were measured. The values of SBP and DBP in the second trimester were obtained from the medical history.

2.3.2 Endothelial function and arterial stiffness

2.3.2.1 Endothelial function assessment. Endothelial function was evaluated by flow-mediated dilation through photoplethysmography, as previously described [8]. Briefly, a photoelectric transducer was placed on the index finger of the left hand. Subsequently, a pneumatic cuff was inflated in the arm to cause a temporary (5 min) interruption of blood flow. During distal ischaemia, the decrease in blood flow at the level of the fingers is associated with a flat line observed on the plot. Then, the pneumatic cuff was deflated. After the release of the ischaemia, the sudden increase in blood flow and shear stress increases endothelium-dependent flow-mediated dilation. The record obtained was scanned to measure the pulse wave amplitude (valley/peak size) using Image J 1.52a (Maryland, USA). Ten consecutive waves were averaged from each phase to compare pre-occlusion vs post-occlusion phases. Endothelial function was defined when the amplitude of post-occlusion waves was higher than pre-occlusion ones. Otherwise, it was classified as "absence of endothelial function."

2.3.2.2 Arterial stiffness assessment. The arterial stiffness index was calculated through photoplethysmography [8]. The procedures were similar to those described above to evaluate endothelial function. A graphic record of ten pulse waves was obtained. Registers obtained from each woman were scanned to determine the arterial stiffness index. Image J 1.52a software was used to calculate the amplitude values [(a*100/b, where a= maximal systolic peak amplitude (mm) and b=maximal diastolic peak amplitude (mm)].

2.3.3 HRV and autonomic function

The HRV was measured in a 5-minute continuous electrocardiogram record at rest sitting (Taurus Touch; JotaTec, Buenos Aires, Argentina) connected to a computer [7]. The distance between R waves of the consecutive beats (RR interval) of the complete DII lead record was obtained. The record was analysed with Kubios HRV 3.1 software (Kuopio, Finland) to measure HRV. In the time domain, HR was analysed. Similarly, the RR interval, the standard deviation of the time that separates two successive beats (SDNN), and the percentage of consecutive beats that differ by more than 50 ms (pNN50) were calculated. In the frequency domain, the low, high, and total frequency powers (LF, HF, and T powers, respectively) and LF/HF ratio were measured. Also, a non-linear geometric analysis using the Poincaré plot scatter was made to calculate the transverse axis (SD1), the longitudinal axis (SD2), and the SD2/SD1 ratio. The Kubios HRV 3.1 software also calculated the mean deviation from typical values of PNS and SNS indexes [9].

2.3.4 Urinary nitrites

Urinary nitrite excretion (NOx) is a non-traumatic indicator of NO bioconversion/bioavailability [7,10,11]. The Griess reaction in a fasting urine sample measured the NOx.

2.4 Ethical considerations

The Ethics Research Committee of the Health Research Directorate from the Ministry of Public Health of Tucumán approved all procedures (Protocol #89). Besides, all participants provided oral and written informed consent to participate before any procedure.

2.5 Data analysis

The data were analyzed using Statistical 5.0 and Graph–Pad Prism 5.02 software. The data were expressed as media±standard error. Descriptive statistics were used to describe the sample's characteristics. Student t-test, Pearson correlation coefficient (Pearson's r), or Chi-squared (χ^2) was used when necessary. $P < 0.05$ values were considered statistically significant.

3. Results

Characteristics of non-GH and GH women are shown in Table 1.

If well no-GH and GH groups showed similar baseline characteristics (Table 1) and a similar number of primiparous women (no-GH: 18 patients vs. GH: 7 patients; χ^2:0.5; p: NS); the birth weight of the children and weeks of gestation until delivery was lower in GH than no-GH (Table 1).

3.1 Hemodynamic variables

In the first trimester, although blood pressure remained at normal values in all patients, the GH group showed higher values of SBP than no-GH (no-GH: 105.8 ± 2.0 mmHg; n = 32 vs. GH: 112.7 ± 3.0 mmHg; n = 11; $p < 0.05$). The DBP was similar in both groups (no-GH: 69.9 ± 1.6 mmHg; n = 32 vs. GH: 72.1 ± 2.2 mmHg; n = 11; p: NS).

Table 1
Baseline characteristics of the studied women.

Variable	no-GH (n = 32)	GH (n = 11)
Age (years)	29.2 ± 0.9	30.3 ± 1.0
Number of previous pregnancies	0,7 ± 0,1	0.7 ± 0.3
Gestational age (weeks)	9.6 ± 0.3	9.8 ± 0.4
Weight (Kg)	72 ± 2	74 ± 2
Height (cm)	165 ± 1	165 ± 2
Body mass index	26.9 ± 0.7	27.2 ± 1.0
Birth weight of the children (g)	3276 ± 63	2780 ± 145 * **
Time of gestation until delivery (weeks)	38.2 ± 0.3	36.4 ± 0.5 * **

* ** : $p < 0001$

In the second trimester, the GH group showed elevated values of SBP (no-GH: 108.7 ± 1.7 mmHg; n = 32 vs. GH: 144.5 ± 1.9 mmHg; n = 11; $p < 0.001$) and DBP (no-GH: 71.8 ± 1.3 mmHg; n = 32 vs. GH: 87.4 ± 1.6 mmHg; n = 11; $p < 0.001$).

3.2 Endothelial function and arterial stiffness

Fig. 1 A shows a typical graphic record of digital pulse/wave plethysmography in patients from no-GH and GH groups at the moment of the study. Endothelial-dependent assay by hyperaemic maneuvers is shown in the top panel in which the left records correspond to the pre-occlusion phase (basal conditions), and the right records correspond to the post-occlusion phase (hyperaemic response). The averages of these responses are shown in Fig. 1B. The endothelial-dependent response was lower in GH than in no-GH. It is important to note that in all no-GH patients, the post-occlusion record was higher than the pre-occlusion record, whereas, in GH, four patients presented a post-occlusion record lower than the pre-occlusion record (χ^2: 12.82; $p < 0.01$).

The arterial stiffness index was increased in GH (no-GH: 40 ± 2% vs. GH: 47 ± 4%;$p < 0.05$). In GH, the arterial stiffness was correlated with SBP (Pearson's r: 0.5594; 95%CI: 0.06106–0.8681; $p < 0.05$). This correlation was not observed in no-GH (Pearson's r: 0.2170; 95%CI: 0.1425–0.5260; p: NS).

3.3 HRV and autonomic function

As shown in Table 2, both groups showed similar values of the variables studied in the time domain. In the frequency domain, LF power was lower in GH (Table 2). When performing the Poincare plot, both groups showed similar values of SD1 (no-GH: 26 ± 2 vs. GH: 28 ± 2; p: NS) and SD2 (no-GH: 41 ± 2 vs. GH: 37 ± 4; p: NS), while the ratio SD2/SD1 was decreased in GH (no-GH: 1.7 ± 0.2 vs. GH: 1.1 ± 0.1; $p < 0.05$).

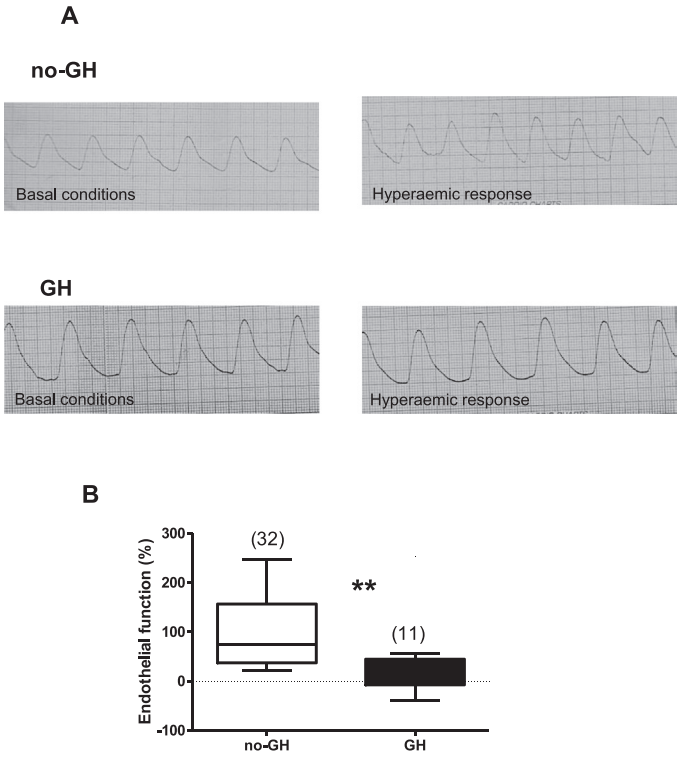

Fig. 1. Endothelial-dependent response assay. **A)** The top panel shows the typical tracings of a no-GH patient (top) and GH (bottom) before (Basal conditions) and after (Hyperaemic response) flow mediated dilatation. **B)** Average of these responses. * *: $p < 0.01$. Data are expressed as mean ± standard error. The numbers of children are given in parentheses.

Table 2
Heart rate variability in the studied women.

Variable	Units	no-GH (n = 32)	GH (n = 11)
Time Domain			
HR	bpm	86.9 ± 1.7	88.2 ± 2.8
RR interval	ms	690 ± 14	678 ± 26
SDNN	ms	35 ± 2	33 ± 3
pNN_{50}	%	13 ± 2	16 ± 6
Frequency Domain			
LF power	ms^2	395 ± 47	228 ± 84 *
HF power	ms^2	478 ± 73	588 ± 176
Total power	ms^2	956 ± 94	844 ± 257
LF/HF ratio	ratio	22 ± 20	0.4 ± 0.1

HR: Heart rate variability; RR interval: distance between R waves of the consecutive beats; SDNN: standard deviation of the time that separates two successive beats; pNN50: percentage of consecutive beats that differ by more than 50 ms; LF: low frequency; HF: high frequency, T: total frequency; * : $p < 0,05$

Fig. 2 A shows typical reports of PNS and SNS indexes obtained in patients from no-GH (top) and GH (bottom) groups. The index averages are shown in Fig. 2B. In both groups, the PNS index showed negative values, and the SNS index showed positive values; however, the inhibition of PNS was lower in GH than in no-GH.

3.4 Urinary nitrites

The NOx was decreased in GH (no-GH: 3.4 ± 0.4 μM/L vs. GH: 0.3 ± 0.1; $p < 0.001$). As shown in Fig. 3, NOx was correlated positively with the PNS index in both no-GH and GH (Fig. 3A) and negatively with the SNS index only in GH (Fig. 3B).

4. Discussion

The main findings of the present study are that women that will later develop pregnancy-induced hypertension presented, during the first trimester, when they still have normal pressure values, modifications in the vascular function that included decreased endothelial function, increased arterial stiffness, and alterations in HRV.

It is known that endothelial function is increased in pregnancy [12]. Agatisa et al. showed that women with a history of preeclampsia had decreased endothelial function [13]. However, to the best of our knowledge, the alterations in endothelial function were not studied in normotensive pregnant women who will develop GH. In the present study, endothelial function decreased previous to developed hypertension. An experimental model of hypertension by a high-fat diet has shown that endothelial dysfunction precedes elevations in blood pressure [14]. Although the pathophysiology of the hypertensive states of pregnancy is still under study, placental vessel dysfunction, in which the spiral arteries become resistance vessels instead of capacitance vessels, plays a fundamental role [15]. Therefore, we could hypothesize that the maternal endothelial function, starting point of the placenta or the maternal vasculature, underlies the pathophysiological mechanisms that will later develop hypertension during pregnancy. The decreased levels of NOx are in agreement with this hypothesis. NOx levels were a non-traumatic indicator of NO bioconversion/bioavailability [7,10] and endothelial function [11]. Moreover, the decreased endothelial function is accompanied by increased arterial stiffness. Although it has already been shown that arterial stiffness is increased in preeclampsia [16], we found that arterial stiffness was increased in the first trimester of pregnancy. Arterial stiffness independently predicts cardiovascular events and mortality in healthy [17] and hypertensive subjects [18]. The increased stiffness in the arterial bed of GH is supported by the fact that, although still within normal values, GH increased SBP. Moreover, the SBP is correlated to arterial stiffness. In this sense, it is widely shown

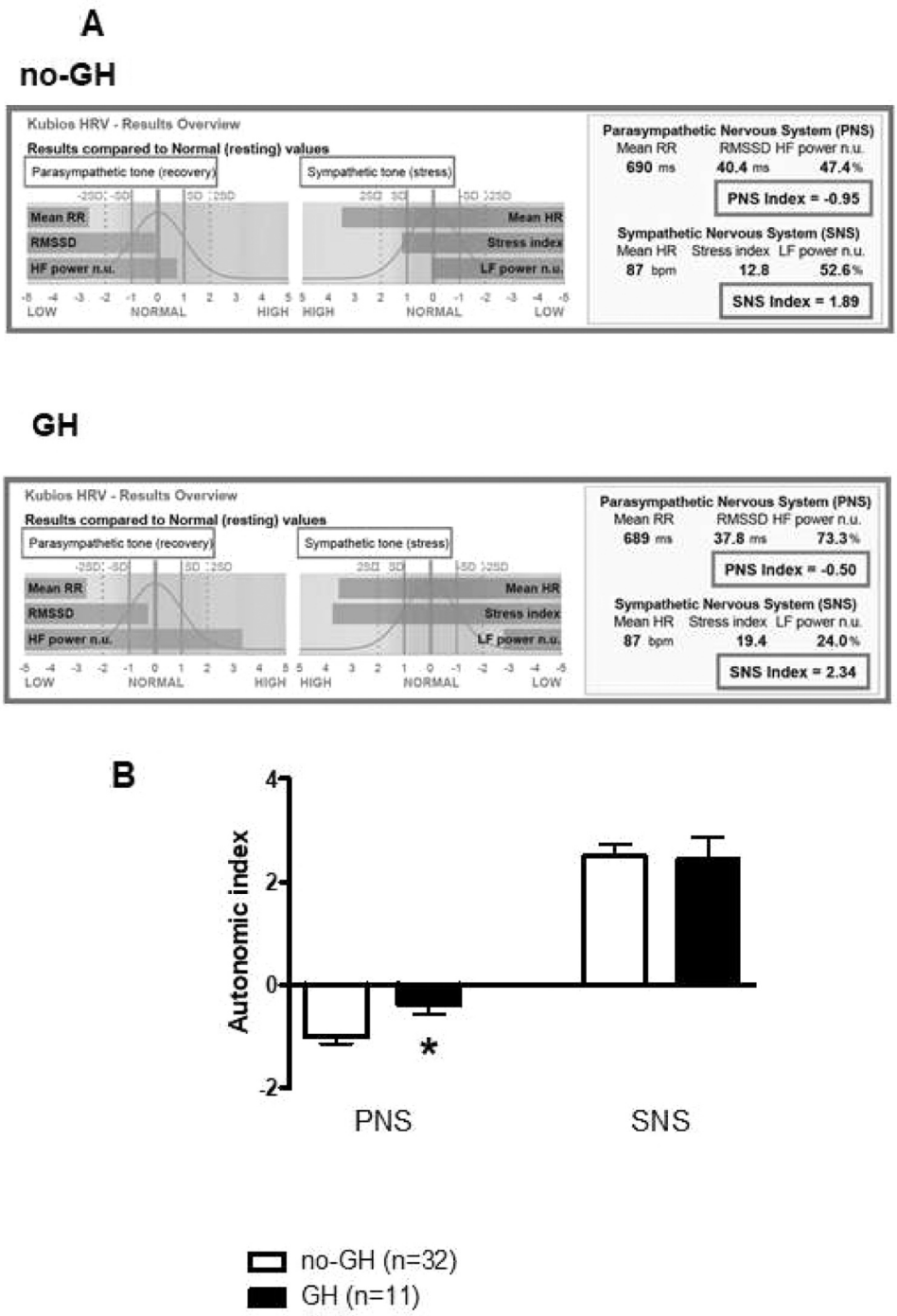

Fig. 2. Autonomic indexes. **A)** Typical report of Kubios HRV 3.1 of the variables used to compute PNS and SNS indexes in a no-GH patient (top) and a GH patient (bottom). **B)** Average of SNS and PNS indexes in the studied women. * : $p < 0.05$. Paired Student t-test. The data are expressed as the mean ± standard error. The numbers of women tested are given in parentheses.

that SBP is more positively correlated to arterial stiffness than DBP [19,20]. Therefore, in this context, the decreased endothelial function and the increased arterial stiffness in GH patients indicate that functional alterations in the maternal vasculature are still present before the clinical phase with overt hypertension.

Briefly, in the HRV study, time domain indices quantify the variability, and frequency domain indices calculate the absolute or relative amount of oscillations within component bands. Non-linear geometric analyses quantify the unpredictability and complexity of the RR interval series [21]. In the present study, we found that, in the frequency domain, GH patients decreased LF without modifications in the time domain. The origin of the LF oscillations is considered to be dominated by SNS [22]. However, LF component also implicated the PNS [23]. Therefore, the decrease in this component could indicate an alteration in the SNS-PNS interrelation more than an isolated stimulation of the SNS. This hypothesis is supported by the non-linear geometric analyses when SD1 and SD2 were similar in both no-GH and GH groups, but the SD2/SD1 ratio was decreased in GH. SD1 could be related to short-term variability mainly caused by respiratory sinus arrhythmia [24]. Although respiratory sinus arrhythmia has been used to index PNS activity [25], this physiologic phenomenon reflects many complex respiratory-circulatory interactions [26]. On the other hand, SD2 describes long-term

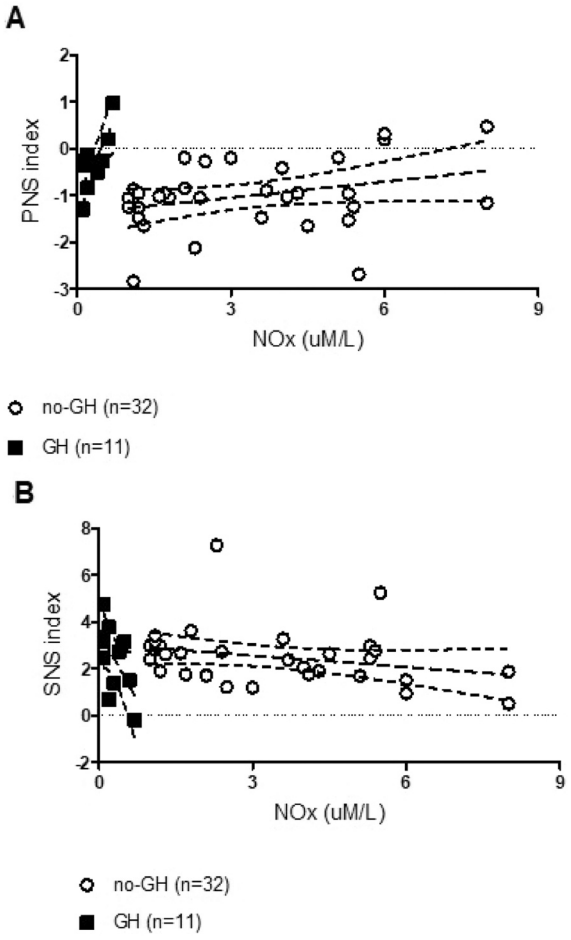

Fig. 3. Correlation between NOx and autonomic indexes **A)** Correlation between NOx and PNS index in no-GH (open circles; Pearson's r: 0.3151; $_{95\%}$CI: −0.03782 to 0.5981; $p < 0.05$) and GH (closed squares; Pearson's r: 0.7701; $_{95\%}$CI: 0.3162–0.9371; $p < 0.01$). **B)** Correlation between NOx and SNS index in no-GH (open circles; Pearson's r: −0.2695; $_{95\%}$CI: −0.5651 to 0.08755; p: NS) and GH (closed squares; Pearson's r: −0.5970; 95%CI: −0.8813 to 0.004584; $p < 0.05$).

variability [24]. Which is not as well defined; SD2 may be inversely related to the SNS modulation. Therefore, the alteration in SD2/SD1 ratio in GH could indicate a modification in the SNS-PNS interrelation to avoid this vasoconstriction trend. As shown in Fig. 2, GH presented less inhibition of PNS. It has been demonstrated that PNS could attenuate endothelial dysfunction [27]. In this context, the correlation between the PNS index and NOx, as observed in this study in no-GH and GH, it was already demonstrated by our laboratory in normal pregnant women [7]. However, the negative correlation between NOx and SNS index is presented only in GH. Therefore, the HRV autonomic indexes results could show the SNS-PNS interrelation modification in these patients.

Non-invasive measurements of endothelial function, arterial stiffness, HRV, autonomic function, and NOx could alert the physician about the possibility of developing gestational hypertension, even with normal pressure values, from the first trimester of pregnancy. Therefore, more research is needed on the role of non-invasive of vascular function studies as predictors of GH.

In conclusion, the development of GH is preceded early in pregnancy by endothelial dysfunction, increased arterial stiffness, and decreased NOx. In this context, there are SNS-PNS interrelation modifications with less inhibition of PNS.

5. Strength and limitations

In this study, the HVR, endothelial function, and arterial stiffness changes produced during the first trimester of pregnancy and their relationship with the development of GH were analyzed; the strict exclusion criteria to rule out potential confounding variables in the measurement of the parameters studied could influence the number of participants, especially in the GH group. In this sense, since the study was conducted in a hospital that is a referral center for pregnant women from the province and the northwest of our country, a selection bias could have occurred, influencing in the percentage of GH patients. However, this selection of patients could also be considered a strength since, ruling out different distractors, highlights the importance of vascular function during the first trimester of pregnancy in the future development of GH. In this sense, future studies with larger sample groups that include women with the exclusion criteria of this work, for example, a history of preeclampsia, could shed light on the criteria proper role on the variables studied.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Butalia S, Audibert F, Cote AM. Hypertension Canada's 2018 guidelines for the management of hypertension in pregnancy. Can J Cardiol 2018;34:526–31.
[2] Shen M; Smith G; Rodger M;Rennicks White R; Walker M; Wu Wen S.Comparison of risk factors and outcomes of gestational hypertension andpreeclampsia PLOS ONE 12(4): e0175914. https://doi.org/10.1371/journal.pone.0175914.
[3] Nzelua D, Dumitrascu-Birisa D, Huntc, Cordinaa M, Kametasa N. Pregnancy outcomes in women with previous gestational hypertension: a cohort study to guide counselling and management. Pregnancy Hypertens 2018;12:194–200.
[4] Lin CC, Lindheimer MD, River Pand Moawad AH. Fetal outcome in hypertensive disorders of pregnancy. Am J Obstet Gynec 1982;142:255–60.
[5] Mori T, Watanabe K, Iwasaki A, Kimura C, Matsushita H, Shinohara K, Wakatsuki A. Differences in vascular reactivity between pregnant women with chronic hypertension and preeclampsia. Hypertens Res 2014;37:145–50.
[6] Moors S, Staaks K, Westerhuis M, Dekker L. Verdurmen k, Oei S, van Laar J. Heart rate variability in hypertensive pregnancy disorders: a systematic review, Pregnancy. Hypertension 2020;20:56–68.
[7] Benvenuto S, Joo Turoni C, Marañón R, Chahla R, Peral de Bruno M. Changes in vascular function and autonomic balance during the first trimester of pregnancy and its relationship with the newborn weight. J Obstet Gynaecol 2021;42:607–13.
[8] Joo Turoni C, Marañón R, Felipe V, Bruno M, Negrete A, Salas N, Bazán de Casella M, Peral, de Bruno M. Arterial stiffness and endothelial function in obese children and adolescents and its relationship with cardiovascular risk factors. Horm Res Paediatr 2013;80:281–6.
[9] Nunan D, Sandercock G, Brodie D. A quantitative systematic review of normal values for short-term heart rate variability in healthy adults. PACE 2010;33: 1407–17.
[10] Elli M, Söylemezoglu O, Erbas D, Bakkaloglu S, Buyan N, Ozkaya O, Hasanoglu E. Plasma and urine nitric oxide levels in healthy Turkish children. Pedia Nephrol 2005;20:1605–9.
[11] Vieira de Oliveira G, Morgado M, Pierucci A, Silveira, Alvares T. A single dose of a beetroot-based nutritional gel improves endothelial function in the elderly with cardiovascular risk factors. J Funct Foods 2016;26:301–8.
[12] Ramsay JE, Simms R, Ferrell W, Crawford L, Greer I, Lumsden M, Sattar N. Enhancement of endothelial function by pregnancy. Diabetes Care 2003;26:475–9.
[13] Agatisa P, Ness R, Roberts J, Costantino J, Kuller L, McLaughlin M. Impairment of endothelial function in women with a history of preeclampsia: an indicator of cardiovascular risk. Am J Physiol Heart Circ Physiol 2004;286:H1389–93.
[14] Oishi J, Castro C, Silva K, Fabricio V, Capelari Cárnio E, Phillips S, Garcia de Oliveira Duarte A, Rodrigues G. Endothelial dysfunction and inflammation precedes elevations in blood pressure induced by a high-fat diet. Systemic arterial hypertension. Arq Bras Cardiol 2018;110:558–67.

[15] Albrecht E, Babischkin J, Aberdeen G, Burch M, Pepe G. Maternal systemic vascular dysfunction in a primate model of defective uterine spiral artery remodeling. Am J Physiol Heart Circ Physiol 2021;320:H1712–23.
[16] Kaihura C, Savvidou M, Anderson M, McEniery C, Nicolaide K. Maternal arterial stiffness in pregnancies affected by preeclampsia. Am J Physiol Heart Circ Physiol 2009;297:H759–64.
[17] Zoungas S, Asmar RP. Arterial stiffness and cardiovascular outcome. Clin Exp Pharm Physiol 2007;34:647–51.
[18] Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. Hypertension 2001;37:1236–41.
[19] Wilson J, Webb AJ. Systolic blood pressure and longitudinal progression of arterial stiffness: a quantitative meta-analysis. J Am Heart Assoc 2020;9:e017804.
[20] Wu S, Jin C, Li S, Zheng X, Zhang X, Cui L, Gao X. Aging, arterial stiffness, and blood pressure association in Chinese adults. Hypertension 2019;73. 893-89.
[21] Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. Front Public Health 2017;Sep 28(5):258. https://doi.org/10.3389/fpubh.2017.00258. PMID: 29034226; PMCID: PMC5624990.
[22] Furlan R, Porta A, Costa F, Tank J, Baker L, Schiavi R, Robertson D, Malliani A, Mosqueda-Garcia R. Oscillatory patterns in sympathetic neural discharge and cardiovascular variables during orthostatic stimulus. Circulation 2000;101:886–92.
[23] Reyes del Paso G, Langewitz W, Mulder L, van Roon A. Duschek. The utility of low frequency heart rate variability as an index of sympathetic cardiac tone: A review with emphasis on a reanalysis of previous studies. Psychophysiology 2013;50:477–87.
[24] Brennan M, Palaniswami M, Kamen P. Do existing measures of Poincaré plot geometry reflect non-linear features of heart rate variability. IEEE Trans Biomed Eng 2001;48:1342–7.
[25] Médigue C, Girard A, Laude D, Monti A, Wargon M, ElghoziJ L. Relationship between pulse interval and respiratory sinus arrhythmia: a time- and frequency-domain analysis of the effects of atropine. Pflu̇gers Arch 2001;441:650–5.
[26] Yasuma F, Hayano J. Respiratory sinus arrhythmia: why does the heartbeat synchronize with respiratory rhythm? Chest 2004;125:683–90.
[27] Li P, Liu H, Sun P, Wang X, Wang C, Wang L, Wang T. Chronic vagus nerve stimulation attenuates vascular endothelial impairments and reduces the inflammatory profile via inhibition of the NF-jB signalling pathway in ovariectomized rats. Exp Gerontol 2016;74:43–55.