Changes in vascular function and autonomic balance during the first trimester of pregnancy and its relationship with the new-born weight

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ABSTRACT
This study aimed to evaluate vascular function changes and autonomic balance during the first trimester of pregnancy and its relationship with the new-born weight. This prospective study performed in pregnant (PG) women and after delivery (not pregnant: NPG) evaluated the endothelial function (EF) and arterial stiffness (AS) by a non-invasive method. We evaluated the heart rate variability (HRV), parasympathetic nervous system (PNS), sympathetic nervous system (SNS) indexes by electrocardiogram (5 min) and the urinary nitrite excretion (NOx). PG increased EF and NOx and decreased AS and HRV. PG decreased the PNS index and augmented the SNS index. The new-born weight positively correlated with the PNS index and augmented the SNS index. The new-born weight positively correlated with the PNS index (Pearson’s $r$: 0.4291; $p <$0.05), NOx, HRV and negatively correlated with AS. In summary, in pregnancy, although haemodynamically, the SNS activation plays a compensatory role, the low rates of PNS inhibition are essential to ensure normal foetal growth.

IMPACT STATEMENT
- What is already known on this subject? In pregnancy, there are adaptive physiological changes in the cardiovascular system that include increases of EF and decreases AS with an SNS activation. The study of HRV lets to predict the SNS and PNS balance and how they affect blood pressure and vascular function.
- What the results of this study add? Although it is known that SNS activation plays a compensatory role in healthy pregnancy, this study adds the critical role of PNS. Early in pregnancy, the low rates of PNS inhibition are essential to ensure normal foetal growth.
- What the implications are of these findings for clinical practice and/or further research? The present results show a potential predictive value of SNS and PNS activity early in pregnancy. It will provide valuable information not only on the pregnant woman’s vascular function but also on the new-born weight.

Introduction
In pregnancy, there are adaptive changes in the cardiovascular system (Facca et al. 2018) that are accompanied by an expansion of plasma volume (Rodger et al. 2015), declining in blood pressure, systemic vasodilatation and an increase in heart rate (HR) (Walters and Lim 1969; Fisher et al. 2002). Furthermore, pregnancy modifies the arterial tone, which is regulated by the endothelial function (EF) through the nitric oxide (NO). The EF is early implicated in the pathophysiology of cardiovascular diseases (Dzau 2004). Also, vascular compliance alterations have been associated with cardiovascular events (Laurent et al. 2001). Therefore, EF and arterial stiffness (AS) could be independent prognostic indicators of cardiovascular damage (Laurent et al. 2006).

EF and AS could be evaluated through a non-invasive method (Kuvin et al. 2003; Itzhaki et al. 2005). Using this methodology, we found a decreased EF without AS alteration in obese adolescents and low birth weight children (Joo Turoni et al. 2013, 2016). Torrado et al. observed an improved EF and aortic stiffness in pregnancy (Torrado et al. 2015) and Savvidou et al. reported that increased AS at 22–24 weeks of gestation predates the pre-eclampsia development (Savvidou et al. 2011). If healthy pregnancy plays a role in EF and AS needs to be investigated.

The beat-to-beat HR variability (HRV) has been used to study the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) balance. Evidence shows that these systems’ changes modify the HRV (Lombardi and Malik 1996; Nunan et al. 2010). Also, the low birth weight in children decreases the HRV, predicting morbidity and mortality (Rakow et al. 2013; Wulsin et al. 2015).

In pregnancy, hypertension (Ferrazzani et al. 2011) and diabetes (Vambergue and Fajardy 2011) modify the new-born weight. Besides, Everett et al. reported that new-born weight is related to maternal HR (Everett et al. 2013).

Therefore, for all mentioned above, we aimed to evaluate vascular function changes and autonomic balance during the...
first trimester of pregnancy and its relationship with the newborn weight.

Materials and methods

A prospective cohort study in women during the first trimester of healthy pregnancy (pregnant: PG) and after 9–12 months of delivery (not pregnant: NPG) was performed. Women were enrolled in the Instituto de Maternidad Nuestra Señora de las Mercedes (Tucumán, Argentina).

Exclusion criteria: Background of cardiovascular disease, hypertension, diabetes, glucose intolerance and smoking. Also, in the current pregnancy, patients that present multiple pregnancies with clinical report of infections or hypertensive disorders, altered uterine Doppler, foetal growth restriction and preterm delivery were excluded.

In NPG, women were studied when presenting a menstrual cycle return. Since it was established that vascular function is improved in the follicular phase (Williams et al. 2001), the studies in NPG were performed 2–3 days after the end of the menstrual cycle. Also, weight, height and gestational age of the new-borns were recorded from the clinical history.

Ethical procedure

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

Hemodynamic variables

Systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean blood pressure (MBP), and HR were measured.

Endothelial function assessment

EF was evaluated through plethysmography, as we previously described (Joo Turoni et al. 2013, 2016). To record and measure the waveforms, we used a plethysmograph connected to an electrocardiograph (Dong Jiang 32A; Chine). Also, to standardise the chart recording, the equipment was calibrated as follows: 1 mm = 0.1 mV velocity: 25 mm/s. The hyperaemic response was obtained by flow-mediated vasodilatation (Joo Turoni et al. 2013). Briefly, a photoelectric transducer was placed on the index finger of the left hand. Previously to the recording phase, women hold their breath for 10 seconds (pre-occlusion phase). Then, the sphygomanometer cuff was insufflated until 50 mmHg above SBP by five minutes (occlusion phase). Subsequently, the sphygmanometer cuff was deflated, and after two minutes, another 10 seconds of apnoea was required (post-occlusion phase). The record obtained was scanned to measure the pulse wave amplitude (valley/peak size) using Image J 1.52a (Bethesda, MD). Ten consecutive waves were averaged from each phase to compare pre-occlusion vs. post-occlusion phases.

Arterial stiffness assessment

The AS index was calculated through the plethysmography system (Joo Turoni et al. 2013). The procedures were similar to those described above to evaluate EF. A graphic record of 10 pulse-waves was obtained with a simultaneous record of the electrocardiogram. Registers obtained from each woman were scanned to determine the AS index. Image J 1.52a software was used to calculate the amplitude values \((a \times 100/b)\), where \(a\) = maximal systolic peak amplitude (mm) and \(b\) = maximal diastolic peak amplitude (mm).

HRV and autonomic function

A continuous electrocardiogram record (five minutes) at rest sitting was acquired (Taurus Touch; JotaTec, Buenos Aires, Argentina) connected to a computer. The distance between R waves of the consecutive beats (RR interval) of the complete DII lead record was obtained. The HRV was analysed with Kubios HRV 3.1 software (Kuopio, Finland). In the time domain, the mean RR interval and the percentage of consecutive beats that differ by more than 50 ms (pNN50) were calculated. Similarly, the standard deviation of the time that separates two successive beats (SDNN) and the HR were analysed. In the frequency domain, the low, high and total frequency powers (LF, HF and T) and LF/HF ratio were measured. Also, Kubios HRV 3.1 software made a non-linear geometric analysis using the Poincaré plot scatter. It graphs the relationship RRn \((x\)-axis\) and RRn + 1 \((y\)-axis\) which let calculate the transverse axis (SD1), the longitudinal axis (SD2) and the SD2/SD1 ratio. Also, it calculates the mean deviation from typical values of PNS and SNS indexes (Nunan et al. 2010).

Urinary nitrates

Urinary nitrite excretion (NOx) is a non-traumatic indicator of NO bioconversion/bioavailability (Elli et al. 2005; de Oliveira et al. 2016). The NOx was measured by the Griess reaction (Marañón et al. 2014) in a fasting urine sample.

Statistical analysis

The data were expressed as mean ± standard error. \(p < .05\) values were considered statistically significant. The Statistical 5.0 and GraphPad Prism 5.02 software (La Jolla, CA) were used for statistical analysis and graphs. A paired Student t-test or Pearson’s correlation coefficient was used when necessary.

Results

In PG, the women’s age was 28.7 ± 0.8 years, and the gestational age in the first trimester of pregnancy was 10 ± 0.2 weeks. As shown in Table 1, both the biochemical screening and the uterine artery Doppler were normal. No women presented protodiastolic notches in uterine artery Doppler. Although in PG, the blood pressure was maintained
into the normal range, a significant decrease of SBP (PG: 104 ± 2 mmHg vs. NPG: 113 ± 3 mmHg; n = 25; p < .001) and DBP (PG: 69 ± 2 mmHg vs. NPG: 74 ± 2 mmHg; n = 25; p < .001) was observed. Likewise, a decrease in pulse pressure (PG: 36 ± 2 mmHg vs. NPG: 40 ± 2 mmHg; n = 25; p < .05) and in MBP in PG (81 ± 2 mmHg vs. NPG 104 ± 2 mmHg; n = 25). The HRV analysis in the time and frequency domains is shown in Table 2. In PG, HR was increased, and the RR interval and SDNN were decreased compared to NPG. In PB, in the frequency domain, HR, RR interval and SDNN did not present any correlation (data not showed). In PG, in the time domain, frequency domain and non-linear geometric analysis variables, no correlation was observed (data not showed).

**Endothelial function and arterial stiffness**

The endothelial-dependent response was markedly increased in PG (PG: 102 ± 19% vs. NPG: 24 ± 4%; n = 25; p < .001), whereas the AS index was decreased (PG: 43 ± 2% vs. NPG: 52 ± 2%; n = 25; p < .001). The women’s age was not correlated with the endothelial-dependent response (PG: Pearson’s r: 0.2057; 95%CI: –0.2063 to 0.5558; p: NS and NPG: 0.06080; 95%CI: –0.3427 to 0.4453; p: NS), and with AS index (PG: Pearson’s r: –0.03598; 95%CI: –0.4252 to 0.3644; p: NS, and NPG: 0.03214; 95%CI: –0.3678 to 0.4220; p: NS).

**HRV and autonomic function**

The HRV analysis in the time and frequency domains is shown in Table 2. In PG, HR was increased, and the RR interval, pNN50, and SDNN were decreased compared to NPG. In the frequency domain, PG showed a reduction in LF, HF and total power, while LF/HF was not modified. The non-linear geometric analysis in PG shows a decrease in both SD1 (PG: 27 ± 2 ms vs. NPG: 41 ± 3; p < .001) and SD2 (PG: 38 ± 3 ms vs. NPG: 60 ± 5; p < .001). Nevertheless, the SD2/SD1 ratio was not modified (PG: 1.4 ± 0.1 vs. NPG: 1.5 ± 0.1; p: NS).

Figure 1(A) shows typical reports of PNS and SNS indexes obtained in PG (top) and NPG (bottom). The index averages are shown in Figure 1(B). 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 SNS index (+282 ± 120%; p < .05).

**Urinary nitrates**

The NOx was increased in PG (PG: 4.5 ± 0.5 uM/L vs. NPG: 1.4 ± 0.1 M/L; p < .001) and positively correlated only with PNS index (Pearson’s r: 0.5748; 95%CI: 0.2323–0.7904; p < .01). In NPG, none correlation between NOx and PNS or SNS indexes was found (PNS vs. NOx: Pearson’s r: –0.0196; 95%CI: –0.4916 to 0.2893; p: NS; and SNS vs. NOx: Pearson’s r: 0.01835; 95%CI: –0.3796 to 0.4106; p: NS).

**Correlation between new-borns weight, height and gestational age and the EF, AS, NOx, and HRV parameters**

In new-borns, the mean birth weight was 3.274 ± 59 g (percentile: 45.0 ± 0.4), the mean birth height was 49 ± 1 cm (percentile: 43.6 ± 6.4) and the gestational age was 38.7 ± 0.2 weeks. All these parameters are considered within normal range.

Similarly, as occurred with EF and AS, the women’s age did not correlate with other parameters.

The EF correlates with neither weight nor height of the new-born in both PG and NPG. However, only in PG, AS index was negatively correlated with new-borns weight (Figure 2(A)). In PG, the NOx was positively correlated with the new-born weight (Figure 2(B)) and the new-born height (Pearson’s r: 0.3995; 95%CI: 0.005029–0.6863; p < .05).

In PG, in the time domain, only pNN50 showed a positive correlation with the new-born weight (Figure 3(A)). Contrary to pNN50, the HR, RR interval and SDNN did not present any correlation (data not showed). In PG, in the frequency domain, HF was positively correlated with the new-born weight (Figure 3(B)). However, in LF, total power, and LF/HF ratio, no correlation was observed (data not showed). Besides, in the non-linear geometric analysis, SD1 was positively correlated with the new-born weight (Pearson’s r: 0.4234; 95%CI: 0.03391–0.7013; Figure 3(C); p < .05). No correlation was observed in the SD2 and SD2/SD1 ratio (data not showed). In NPG, in the time domain, frequency domain and non-linear geometric analysis variables, no correlation was observed (data not showed).

In PG, PNS index was positively correlated with the new-borns weight (Pearson’s r: 0.4291; 95%CI: –0.04078 to 0.7048; p < .05) and height (Pearson’s r: 0.4243; 95%CI: 0.03500–0.7019; p < .05). SNS index showed no correlation with the same factors (weight: Pearson’s r: –0.3415; 95%CI: –0.6491 to 0.06212; p: NS and height: Pearson’s r: –0.1266; 95%CI: –0.4970 to 0.2828; p: NS). In NPG, there is no correlation between PNS and SNS indexes with weight or height (data not shown).

### Table 1. Biochemical screening and uterine artery Doppler of the first trimester in the studied women (n = 25).

| Variable                  | Value       |
|---------------------------|-------------|
| Biochemical screening     |             |
| Haematocrit               | 37.1 ± 0.4% |
| Haemoglobin               | 12.1 ± 0.1 g/dL |
| Fasting glucose           | 82.6 ± 0.9 mg/dL |
| Creatinine                | 0.7 ± 0.03 mg/dL |
| GOT                       | 15.2 ± 0.9 U/L |
| GPT                       | 16.4 ± 0.6 U/L |
| Urea                      | 7.7 ± 0.673 mg/dL |
| Platelets                 | 2,683,887 ± 7783/mm³ |
| Uric acid                 | 3.0 ± 0.1 mg/dL |
| Uterine artery Doppler    |             |
| Right uterine artery PI   | 1.5 ± 0.1   |
| Left uterine artery PI    | 1.6 ± 0.1   |
| Mean PI                   | 1.5 ± 0.1   |
| Percentile of PI          | 56.5 ± 3.3  |

### Table 2. Heart rate variability in the studied women (n = 25).

| Variable                  | Units          | PG          | NPG          |
|---------------------------|----------------|-------------|--------------|
| Time domain               |                |             |              |
| HR                        | bpm            | 90 ± 2      | 76 ± 1***    |
| RR interval               | ms             | 687 ± 17    | 792 ± 14***  |
| pNN50                     | %              | 13 ± 3      | 30 ± 3***    |
| SDNN                      | %              | 33 ± 2      | 49 ± 3***    |
| Frequency domain          |                |             |              |
| LF                        | ms²            | 397 ± 94    | 1029 ± 257*  |
| HF                        | ms²            | 470 ± 78    | 1312 ± 381*  |
| Total power               | ms²            | 963 ± 152   | 2530 ± 596** |
| LF/HF ratio               | ratio          | 0.9 ± 0.1   | 1.2 ± 0.3 NS  |

*p < .05; **p < .01; ***p < .001.
Discussion

The main findings of the present study are: (1) in early pregnancy there is an increase in EF and a decreased AS and HRV, (2) these changes are accompanied by an increased SNS index and a decreased PNS index and (3) PNS index was positively correlated with the new-born weight.

During the first trimester of pregnancy, there is a decreased blood pressure due to a fall in the peripheral vascular resistance through dependent-endothelial vasodilation (Leiva et al. 2016). In our study, PG showed a strong EF which decreases after delivery (NPG) with an increased NO release supporting the fact that in pregnancy, the EF is mainly NO-dependent (Ramsay et al. 2003; Tanaka et al. 2015).

Healthy pregnancy enhances EF (Ramsay et al. 2003; Boeldt and Bird 2017) and reduces AS during all adaptation processes (Mahendru et al. 2014). In PG, we found a decrease in AS, which was described by other authors, as well (Macedo et al. 2008). It could be due to smooth muscle tone or vascular remodelling in different vascular beds (Edouard 1998) where the extravillous trophoblast cells mediate the uterine decidual spiral arterioles remodelling (Chen et al. 2012). Hence, the changes in EF and AS in the peripheral beds would be involved in the decreased BP at this stage (Mahendru et al. 2014).

The HRV has been used to study the sympathetic and parasympathetic system’s balance. Although different studies indicate that the foetal environment plays an essential role in
developing cardiometabolic risk later in life, few studies of the impact of autonomic balance and intrauterine growth have been performed. Furthermore, some of its results showed conflicting data (Lahiri et al. 2008).

In our study, we found a decreased HRV in PG. In the time domain, quantifying the amount of HRV, we observed that HR, RR interval, pNN50 and SDDN were reduced (Table 2). Interestingly, only pNN50 was positively correlated with the newborn weight. As pNN50 is an indicator of vagal tone (Koenig et al. 2015), it suggests that the degree of vagal tone inhibition during early pregnancy is related to the newborn weight in the child after delivery. On the other hand, decreased SDNN is an indicator of increased SNS activity (Tarvainen et al. 2014). Since the evidence showed that in pregnancy, the sympathetic activity is increased, it is not surprising that SDNN was reduced. In the frequency domain, which calculates the amount of signal energy within each component band, LF, HF and total power were also decreased (Table 2).

HF is a specific PNS indicator, whereas LF has associated with both SNS and PNS activity (Malik and Camm 1993). It also indicates the role of the inhibition of vagal tone on the newborn weight. Regarding the changes in the non-linear geometric analysis, SD1 (an indicator of PNS activity) and SD2 (inverse SNS activity indicator) were decreased in PG (Kamen et al. 1996; Toichi et al. 1997). Also, PG showed a modified SNS/PNS balance. Recently, Iacobaeus et al. demonstrated that pregnancy produces a simultaneous cardiac and arterial adaptation associated with autonomic balance (Iacobaeus et al. 2018). Here, we found a higher increase in the SNS index, where the sympathetic system maintains maternal blood flow through increased minute volume. Therefore, both branches (SNS and PNS) play a role in the hemodynamic regulation during early pregnancy.

In PG, we found that the newborn weight was associated with AS, NOx and HRV. Everett demonstrated that the birth weight was correlated to the HR; however, these findings were in the mid-trimester maternal, and the group of the domain that characterizes the HRV components was not evaluated (Everett et al. 2013).

In children, HRV is negatively correlated with birth weight (Rakow et al. 2013). Also, in postconceptional age, the HRV is related to intrauterine maturation of the autonomic cardio regulatory activity (Sahni et al. 2000). In this sense, we hypothesise that PNS regulation plays a vital role in the mother–child binomial hemodynamic. This hypothesis is
supported because only PNS index correlates with the newborn weight. Furthermore, the newborn body weight was positively correlated with HF and SD1, PNS activity indicators (Malik and Camm 1993; Kamen et al. 1996). The NOx positive correlation with the newborn weight could be due to the PNS effect on the NO bioavailability (Li et al. 2016).

In summary, our study shows that the parasympathetic branch inhibition would be responsible for hemodynamic regulation during the first trimester of pregnancy. It is essential to ensure normal foetal growth. In the counterregulatory PNS/SNS balance, an increase in NO release and a decrease in the maternal peripheral vascular resistance may be implicated. Therefore, the evaluation of the PNS index may help as a clinical parameter in order to evaluate the hemodynamic control during early pregnancy and predicts the newborn weight.

Disclosure statement

All authors have no conflicts of interest to declare.

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