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ORIGINAL ARTICLE

The dynamics of autonomic nervous system activity and hemodynamic changes in pregnant women

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Abstract

OBJECTIVE: The purpose of this research was to assess the dynamics of autonomic nervous system(ANS) and hemodynamic activity changes during uncomplicated pregnancy.
METHODS: We enrolled 36 pregnant women (mean age 29±4.8years) and a control group of 10 non-pregnant women (mean age 25.9±0.88years). The examination was performed in the 1st, 2nd, and 3rd trimester. Continuous registration of BP, ECG, and cardioimpedance was performed with Task Force Monitor 3040i. ANS activity was measured using the following parameters: HRV, BPV, BRS at rest, and in response to autonomic tests.
RESULTS: Compared to the 1st trimester, an increase in HR (73 vs. 92 bpm; $p<0.001$) and mean BP (80 vs. 85 mmHg, $p<0.01$) was observed in the 3rd trimester. In the 1st trimester, the BRS of pregnant women was insignificantly higher than in the controls (24.8 vs. 22.3 ms/mmHg); subsequently, it decreased significantly, to 13.4 ms/mmHg in the 3rd trimester ($p=0.0004$). An increase in nLF (39.57±13.75 vs. 58.73±15.55; $p=0.001$) and LF/HF ratio (1.03±0.76 vs. 1.85±0.8; $p<0.00002$) was revealed in HRV analysis conducted in the 3rd trimester, as compared to the 1st trimester, along with a decrease in nHF (60.43±13.71 vs. 41.26±15.55; $p<0.001$). An increase in LF/HF-sBPV (1.05±0.48 vs. 1.58±0.44; $p=0.01$) was recorded in BPV analysis at rest in the 3rd trimester as compared to the respective 1st trimester value.
CONCLUSION: Our findings suggest that pregnancy is associated with dynamic changes in autonomic balance, namely doubled dominance of the sympathetic component. Hypervolemia seems the major factor responsible for autonomic and hemodynamic changes observed during pregnancy, as it causes an increase in BP and simultaneous decrease in BRS.

Abbreviations

BRS	- baroreceptors activity
BP	- blood pressure
BPV	- blood pressure variability
ECG	- electrocardiography
HF	- high frequency
HR	- heart rate
HRV	- heart rate variability
LF	- low frequency
TFC	- total fluid content

INTRODUCTION

The autonomic nervous system (ANS) is responsible for cardiovascular, gastrointestinal, and urinary system control. Pregnancy is associated with adaptive changes in the functioning of those systems, in particular in maternal hemodynamics, which is accompanied by changing levels of various vasoactive hormones and metabolites. These changes are detectable very early, even at 4th week of gestation, and are nearly completed in the first half of pregnancy.

The results of previous studies suggest that maternal hemodynamic adaptation to pregnancy is most likely triggered by a primary fall in systemic vascular tone. According to the published data, cardiac output raises during pregnancy as the result of the fall in systemic vascular resistance and an expansion of blood volume that lead to a decreased afterload and an increased preload, respectively. It has been proposed that hemodynamic changes taking place during pregnancy occur through autonomic control mechanisms, but the exact role of the autonomic nervous system in those adaptation processes is poorly understood (Fu & Levine 2009; Ekholm *et al.* 1997; Szymanska *et al.* 2008). Vascular tone is to a large extent modulated by the activity of the sympathetic nervous system interrelated to the release of placental hormones (Heiskanen *et al.* 2008; Rang *et al.* 2002; Lucini *et al.* 1999).

In contrast to the sympathetic activation, peripheral vascular resistance was found to be even lower in normal healthy pregnant women, during their late pregnancies. This finding suggests that the transduction of sympathetic impulse into vascular resistance is blunted during pregnancy. The mechanisms responsible for the blunted vascular transduction during pregnancy are unknown. The results of previous studies suggest that estrogens may decrease the transduction of sympathetic traffic into vascular resistance through local mechanisms (Metsaars *et al.* 2006).

The results of previous studies of cardiac autonomic function in human pregnancy are inconclusive and supplied fractional results by investigating the autonomic system in different gestational stages. The autonomic nerves, as well as end-organ responsiveness and circulatory hemodynamics are involved, and only indirect information about the complex cardiovascular reflex arc can be assessed by analyzing the heart rate and blood pressure responses (Moertl *et al.* 2009; Faber *et al.* 2004). The purpose of this study was the evaluation of the sequential and dynamic changes of autonomic nervous system activity, based on analysis of heart rate and blood pressure variability and autonomic tests (the Valsalva maneuver, the cold pressor and the deep breathing tests, i.e. cardiovascular reflex tests) and hemodynamics throughout the entire pregnancy.

MATERIALS & METHODS

The study included 36 pregnant women (mean age 29±4.8 yrs) and 10 age- and gender-matched healthy volunteers (non-pregnant women; mean age 29.5±5.2 yrs). All the measurements were taken three times: in the 1st (6–12 week), 2nd (18–24 week), and 3rd trimester (30–35 week). The characteristics of the investigated group are presented in Table 1.

The exclusion criteria from the study were: diabetes mellitus, obesity, cardiovascular diseases (hypertension, coronary artery disease, valvular heart disease), gastrointestinal pathologies (e.g. inflammatory bowel disease), and renal or gynecological pathologies. Moreover, the patients were excluded if they had any known cardiac arrhythmias or have been taking medications that could interfere with the HRV measurement, such as calcium-channel blockers, beta-blockers, and tricyclic antidepressants.

Study protocol

HRV, BPV, BRS. The autonomic activity was assessed based on the heart rate variability (HRV), blood pressure variability (BPV), and baroreflex sensitivity (BRS). After an overnight fast, continuous measurements of the ECG signal, beat-to-beat blood pressure, and cardio-impedance signal were taken with Task Force Monitor 3040i (CNSystem, Austria). Subsequently, the recorded ECG signal was subjected to frequency analysis (based on fast Fourier transformations). The following parameters were considered: TP – total power, i.e. the variance of RR intervals over the selected time interval, VLF – power of very low frequency component (0.0033–0.04 Hz), LF power – power of the low frequency component (0.04–0.15 Hz), HF power – power of high frequency component (0.15–0.4 Hz), LF/HF ratio – ratio of LF power to HF power, and normalized units: nLF and nHF (Pinna *et al.* 2007; Maestri *et al.* 2007).

Tab. 1. Clinical characteristic of the investigated women.

Trimester	1st (n=35)	2nd (n=32)	3rd (n=22)	Non-pregnant (n=10)	*p*-value
Age	29±4.08	29±4.08	29±4.08	25.9±0.876	0.02
Height [m]	1.68±0.07	1.67±0.07	1.68±0.07	1.664±0.6	NS
Weight[kg]	63.8±9.95	68.2±10	75±11.3	56.9±5.259	0.03
BMI [kg/m^2]	22.6±2.82	24.3±3.04	26.4±3.24	20.52±1.2	0.00002

Autonomic tests. All tests were performed in the morning under standard conditions, in a quiet and relaxing environment, after 12 hours of overnight fast (Jaradeh & Prieto 2003).

Deep breathing test (DB)

The DB test was chosen as a method of estimating parasympathetic activity (Zygmunt & Stanczyk 2010). Regular deep breathing at the rate of 6 breaths per minute (5 seconds inspiration and 5 seconds expiration) was performed to estimate: ΔI–E – the difference between maximal heart rate during inspiration and the minimal heart rate during expiration, E/I ratio – mean ratio of the longest RR interval during expiration to the shortest RR interval during inspiration, counted from 6 consecutive cycles, DBD – the deep breath difference, RSA – respiratory arrhythmia index, and parameters of HRV analysis.

Valsalva maneuver

This maneuver provides an excellent test of the integrity of both arterial and cardiopulmonary baroreflex arc (Ekholm *et al.* 1996; Zygmunt & Stanczyk 2010; Schönauer *et al.* 2008). The Valsalva test comprises an abrupt transient voluntary elevation of intra-thoracic and intra-abdominal pressure provoked by straining. The investigated subject blows into a mouth-piece of the manometer to 40 mmHg for 15 s, with continuous ECG and BP monitoring before, during and after the procedure. For evaluating the Valsalva test, the Valsalva ratio (VR), which is the index of cardiac parasympathetic efferent activity, is used. Arterial pressure elevations after the release of Valsalva straining provide acceptable estimates of preceding sympathetic nerve responses and control mechanisms (Ekholm & Erkkola 1997; Rang *et al.* 2002).

Cold Pressor Test

The Cold Pressor Test was performed by placing the subject's hand, up to the wrist, in ice water (0–4 °C) for 120 s. This elicits an instantaneous local and generalized vasoconstriction in the skin and the skeletal muscles, which is not only a direct effect of cold on the local skin vessels, but also a result of pain-activating spinal cord and hypothalamic reflexes. The heart rate increases to a peak value within the first 30 s and returns to baseline level up to one minute. Due to an increase in total peripheral resistance, arterial pressure increases, with maximum in the second minute of the test. The pressor response is strongly correlated with the increase of muscle sympathetic neural activity, as measured by direct recordings of the latter (Mourot *et al.* 2009).

The study conformed to ethical guidelines outlined in the Declaration of Helsinki and was approved by the Jagiellonian University Bioethical Committee (decision no. KBET/151/B/2011). All subjects included in the study were instructed about its purpose and gave their written informed consent to participate in the project.

Statistics

Database management and statistical analyses were performed using the Statistica for Windows, version 7.0 PL (StatSoft the Inc., Tulsa OK, USA). All values are expressed as percentages or means ± SDs. Normal distribution of the analyzed variables was verified with Shapiro-Wilk test. In the case non-normally-distributed variables, they were subjected to a logarithmic transformation prior to further analysis. Depending on a distribution, either the paired Student's t-test or Wilcoxon's signed rank test were used for intergroup comparisons of quantitative variables. Associations between HRV, BPV and hemodynamics parameters were studied with the Spearman's correlation coefficients. Statistical significance of all the tests was set at $p<0.05$.

RESULTS

Hemodynamic changes:

Compared to the 1st trimester, a significant increase in maternal heart rate HR was documented in the 3rd trimester (73 vs. 92 bpm; $p<0.001$). Although mean blood pressure remained generally stable, a significant increase in mBP (80 vs. 85 mmHg, $p=0.002$), and a significant decrease in diastolic blood pressure (70 vs. 67.5 mmHg; $p=0.02$) were observed in the 3rd and 2nd trimester, respectively. In contrast, systolic blood pres-

Tab. 2. Hemodynamic measurements taken at rest in pregnant and non-pregnant women.

Trimester	1st	2nd	3rd	Non-pregnant	*p*-value
HR [bpm]	73±6.9	80.8±9.08	92±14*	75±10&	0.000001&*
dBP [mm Hg]	70±8.2	67.5±7.97	73±8.1	75±7.8	0.0207
sBP[mm Hg]	108±12	106±10.4	113±10	112±6.1	0.0994
mBP [mm Hg]	80±9.3	78.4±8.72	85±8.3*	89±8.4	0.0025*
BRS [ms/mmHg]	24.8±12.1	15.6±7.7*	13.4±7.0*	22.3±11.2&	0.0004*&
TFC [1/kOhm]	28.0±5.9	32.9±10*	28.8±6.5	27.1±10.4#	0.02*#

* – significant differences between the 1st and 2nd or 3rd trimester; # – significant differences between the controls and pregnant women in the 1st trimester; & – significant differences between the controls and pregnant women in the 3rd trimester. HR – heart rate; dBP – diastolic blood pressure; sBP – systolic blood pressure; mBP – mean blood pressure; BRS – baroreflex sensitivity, TFC – Total fluid content.

sure remained unchanged throughout the entire pregnancy (Table 2).

Whereas BRS of pregnant women did not differ significantly from that of the controls (24.8 vs. 22.3 ms/mmHg) in the 1st trimester, it decreased significantly, to 13.4 ms/mmHg, in the 3rd trimester (p=0.0004). Similar changes of BRS were noted in during DB and CPT (Table 3). In the 2nd trimester, the total fluid content (TFC) of pregnant women was higher than in the controls; a gradual increase in this parameter was observed between the 1st and 2nd trimester (Table 2).

HRV

Compared to the 1st trimester, an increase in nLF (39.57±13.71 vs. 58.73±15.55; p<0.001) and LF/HF ratio (1.03±0.76 vs. 1.85±0.96; p<0.002) was documented in HRV analysis in the 3rd trimester, along with a decrease in nHF (60.43±13.71 vs. 41.28±15.55; p<0.001).

No significant differences in the HRV response to DB were observed in pregnant women, either compared to the controls or on trimester-to-trimester comparisons. The only exception pertained to HF in the 3rd trimester which was significantly lower than in the 1st trimester (Table 4).

A significant decrease in HF and LF values was observed in response to CPT in the 3rd trimester (Figure 1). The CPT-provoked decrease turned out to be most pronounced in the case of HF. The changes of HRV indices pointed to a gradual increase of sympathetic activity and the blunted parasympathetic component.

BPV

Compared to the 1st trimester, an increase in diastolic LF/HF-dBPV (1.81±0.81 vs. 1.15±0.42; p=0.02) and systolic LF/HF-sBPV (1.12±0.42 vs. 1.81±0.92 p=0.01) was observed in the 3rd trimester in BPV analysis conducted at rest (Figure 2).

Tab. 3. Changes in baroreceptor activity (BRS) documented at rest and following DB and CPT in pregnant and non-pregnant women.

Trimester	1st	2nd	3rd	Non-pregnant	*p*-value
At rest					
BRS [ms/mmHg]	24.8±12.1	15.6±7.7*	13.4±7.0*	22.3±11.2&	0.0004*&
During DB					
BRS [ms/mmHg]	21.9±7	18.3±7.3	16.37±17.7*	19.58±8.36	0.01*
During CPT					
BRS [ms/mmHg]	18.76±8.2	16.8±7.3	13.2±9.5*	16.5±9.36	0.01*

* – significant differences between the 1st and 2nd or 3rd trimester; & – significant differences between the controls and pregnant women in the 3rd trimester. BRS – baroreflex sensitivity.

Tab. 4. Changes in HRV parameters changes observed at rest and during DB test in pregnant and non-pregnant women.

Trimester		1st	2nd	3rd	Non-pregnant	*p*-value
Rest	TP [ms^2]	6.81±0.84	6.53±1.25	6.93±2.05	7.02±0.78	NS
	LF [ms^2]	5.58±0.85	5.36±1.07	5.13±1.83	6.28±0.77	0.02&
	HF [ms^2]	6.04±1.09	5.20±1.30	4.6±2.43	5.8±1.02	0.003*
	nLF	39.57±13.71	52.71±14.23	58.73±15.55	58.69±15.43	0.0002*
	nHF	60.43±13.71	47.28±14.23	41.26±15.55	41.31±15.43	0.00002*/0.0007#
	LF/HF	1.03±0.76	1.38±0.84	1.85±0.96	1.42±0.68	0.04&/0.00002*
DB test	TP [ms^2]	8.67±1.07	8.12±1.14	7.5±1.65	8.53±0.7	0.003*
	LF [ms^2]	8.55±1.11	7.93±1.34	6.44±1.47	8.38±0.81	0.0001&/0.0007*
	HF [ms^2]	5.72±1.02	5.36±1.01	4.31±1.71	5.61±0.98	0.0004*/0.02&
	nLF	86.38±5.37	84.16±8.71	83.86±8.39	86.77±7.53	NS
	nHF	13.61±5.37	15.83±8.71	16.13±8.39	13.22±7.53	NS
	LF/HF	15.14±13.31	13.88±14.01	8.67±8.44	18.45±21.92	NS

* – significant differences between the 1st and 2nd or 3rd trimester; # – significant differences between the controls and pregnant women in the 1st trimester; & – significant differences between the controls and pregnant women in the 3rd trimester. TP – total power – the variance of RR intervals over the selected time interval, LF – power of the low frequency component (0.04–0.15 Hz), HF – power of high frequency component (0.15–0.4 Hz), LF/HF ratio – ratio of LF to HF power; nLF and nHF – normalized units of LF and HF.

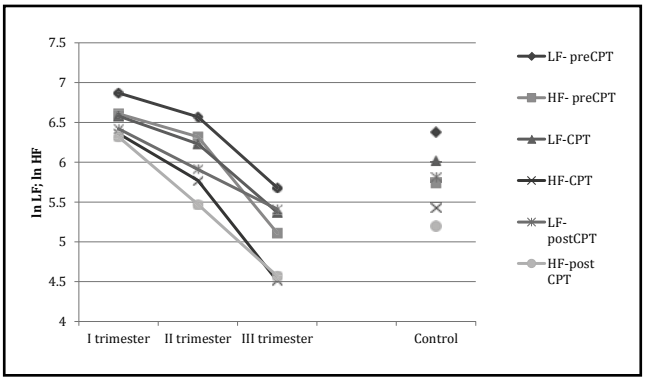

Fig. 1. Changes in heart rate variability (HRV) parameters, LF and HF, documented before, during and after CPT at various stages of pregnancy and among non-pregnant women. CPT – cold pressor test.

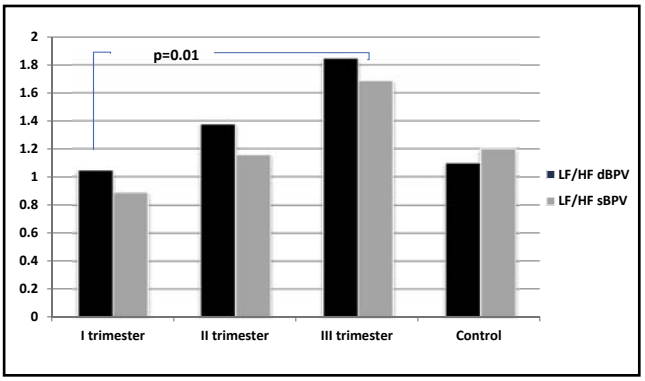

Fig. 2. Changes in blood pressure variability (BPV) parameter LF/HF ratio at rest documented at various stages of pregnancy and among non-pregnant women. LF/HF-dBPV-ratio in diastolic BPV LF/HF-sBPV-ratio in systolic BPV.

A decrease in post-DB test values of normalized diastolic LFnu-dBPV (63.22±11.74 vs. 54.82±9.31 p=0.01) and systolic LFnu-sBPV (57.21±11.78 vs. 49.53±7.78 p=0.016) was documented between the 1st and 3rd trimester of pregnancy.

Furthermore, a gradual decrease in post-CPT diastolic LF-dBPV and HF-dBPV, and systolic LF-sBPV and HF-sBPV was observed between the 1st and 3rd trimester, along with significant increase in LF/HF-dBPV and LF/HF-dBPV ratios (Table 5). The changes documented in BPV analysis corresponded to a gradual increase in sympathetic activity and weaker response to additional sympathetic stimulation.

Autonomic tests

The indices of DB test, E/I ratio, ΔI–E, DBD, and RSA, were normal; however, a significant decrease in their values was documented in the 3rd trimester. Similar

Tab. 5. Changes in BPV parameters documented before, during and after CPT in pregnant and non-pregnant women.

Trimester		1st	2nd	3rd	Non-pregnant	*p*-value
Before CPT	LF–dBPV	2.52±0.78	2.50±1.12	1.77±0.54	3.11±2.35	0.0005*/0.04&
	HF–dBPV	0.73±0.29	0.76±0.42	0.45±0.14	0.82±0.58	0.001*/0.016&
	LF–sBPV	2.94±0.89	2.88±1.78	2.36±0.96	3.70±2.15	NS
	HF–sBPV	0.93±0.49	0.92±0.72	0.58±0.17	1.25±1.55	0.001*
	LF/HF–dBPV	1.15±0.42	1.21±0.59	1.81±0.81	1.49±0.44	0.02*
	LF/HF–sBPV	1.12±0.42	1.22±0.54	1.81±0.92	1.51±0.46	0.01*
CPT	LF–dBPV	2.38±0.69	2.45±1.14	1.72±0.57	2.37±1.04	0.001*/0.006&
	HF–dBPV	0.71±0.27	0.73±0.43	0.44±0.13	0.86±0.64	0.00005*/0.002&
	LF–sBPV	2.76±0.91	2.74±1.85	2.22±0.85	3.25±1.65	0.04*
	HF–sBPV	0.93±0.63	0.93±0.81	0.59±0.17	1.13±0.94	0.01*/0.04&
	LF/HF–dBPV	1.19±0.51	1.47±0.72	2.43±1.78	1.58±0.51	0.01*/0.047&
	LF/HF–sBPV	1.16±0.48	1.43±0.67	2.28±1.58	1.57±0.44	0.01*/0.047&
After CPT	LF–dBPV	2.25±0.66	2.31±1.65	1.69±0.54	2.46±1.03	0.001*/0.03&
	HF–dBPV	0.71±0.26	0.72±0.50	0.44±0.13	0.79±0.62	0.004*/0.038&
	LF–sBPV	2.61±0.85	2.56±1.95	2.18±0.89	3.27±1.93	0.04&
	HF–sBPV	0.94±0.57	0.91±0.83	0.59±0.17	1.33±1.66	0.004*/0.005&
	LF/HF–dBPV	1.02±0.39	2.31±5.7	2.36±1.66	1.81±1.37	0.007*/0.028&
	LF/HF–sBPV	0.98±0.36	1.28±0.58	2.25±1.52	1.71±1.18	0.005*/0.02&

* – significant differences between the 1st and 2nd or 3rd trimester ; # – significant differences between the controls and pregnant women in the 1st trimester; & – significant differences between the controls and pregnant women in the 3rd trimester. LF–BPV – systolic or diastolic power of the low frequency component (0.04–0.15 Hz), HF–BPV – systolic or diastolic power of high frequency component (0.15–0.4 Hz), LF/HF–BPV – systolic or diastolic ratio of LF to HF power.

changes occurred in response to Valsalva maneuver (VM) in pregnant women. All these findings point to blunted parasympathetic activity.

A significant decrease in the indices of CPT, i.e. Δ sBP, Δ dBP, and Δ HR, was observed in the 3rd trimester as compared to the respective values determined in the 1st trimester and among the controls (Table 6). These changes corresponded to a gradual decrease in sympathetic response to sympathetic stimulation.

Correlation

In the 2nd trimester, TFC correlated positively with systolic and diastolic blood pressure variability parameters: LF/HF-sBPV (r=0.39; *p*=0.02), LFnu-dBPV (r=0.34; *p*=0.03), and LF/HF-dBPV (r=0.4; *p*=0.01).

DISCUSSION

The aim of this study was to evaluate the pathophysiological importance of the dynamics of autonomic nervous system activity and hemodynamic activity among pregnant women. Consistently with our hypotheses, we observed that:

In the 2nd trimester, the total fluid content (TFC) of pregnant women was higher than in the controls, and gradually increased between the 1st and 2nd trimester.

The values of sympathetic activity indices, LF, nLF, and LF/HF, were higher in the 3rd than in the 1st trimester.

The changes in BPV indices occurring between the 1st and 3rd trimester, namely an increase in diastolic and systolic LF/HF, corresponded to a gradual increase in sympathetic activity.

A gradual decrease in sympathetic activity and blunted response to parasympathetic activation are observed between the 1st and 3rd trimester as a result of the autonomic response tests (DB, VM).

Blunted response to sympathetic activation during CPT was documented in the 3rd trimester of pregnancy.

The most prominent cardiovascular changes take place in early pregnancy. Potential mechanisms responsible for the decrease in systemic vascular resistance observed during pregnancy in humans include the development of a new uteroplacental vascular circuit, the retention of fluids leading to expansion of blood volume, and primary systemic/venous vasodilation. However, these mechanisms are not sufficient to explain the systemic decrease in vascular resistance, since most of the changes occur outside the uteroplacental circulation. Vascular tone is to a large extent modulated by the activity of the sympathetic nervous system. However, increased activity of the latter in advanced pregnancy is reflected by a decrease in peripheral resistance (Heiskanen *et al.* 2008; Rang *et al.* 2002; Lucini *et al.* 1999). The mechanism underlying the primary reduction in peripheral vascular resistance in early pregnancy is unclear, but the endothelial release of nitric oxide has been proposed as a major determinant of this phenomenon. In addition, cardiac output increases very early in the pregnancy as a result of increased heart rate and stroke volume. Increased shear stress, resulting from augmented flow in both systemic and resistance arteries, may be reflected by enhanced release of nitric oxide (Fu & Levine 2009; Swiatek & Chazan 1999; Ekholm *et al.* 1997). Stepwise expansion of blood volume is postulated a significant determinant of these changes; it is observed as early as in the 4th week of gestation, causes an increase in preload, and precedes the activation of the RAS system and elevation of the progesterone level (Metsaars *et al.* 2006). We observed an increase in total fluid contents (TFC) in the 2nd trimester, with a return to the baseline level in the 3rd trimester. These findings are partially consistent with the results published by Lukaski *et al.*

Tab. 6. Parameters of autonomic system tests documented in pregnant and non-pregnant women.

Trimester		1st	2nd	3rd	Non-pregnant	*p*-value
DB test	E/I	1.39±0.16	1.32±0.13	1.12±0.43	1.40±0.16	0.002*/0.01&
	ΔI – E	19.7±2.4	13.21±3.2	10.21±3.2	22.3±2.8	0.002*&
	DBD	221±79	184±84	154±94	232±69	0.002*&
	RSA	0.24±0.08	0.20±0.06	0.19±0.06	0.28±0.08	0.002*&
Valsalva test	VR ratio	2.12±0.53	1.95±0.71	1.31±0.21	1.33±0.17	0.000004*#
Cold pressor test	Δ sBP	11.25±7.66	11.71±15.08	8.86±5.4&	13.2±8.36	0.01&
	Δ dBP	7.11±5.04	8.27±10.2	6.60±8.9	8.22±5.66	NS
	Δ HR	20.8±8.4	18.6±8.4	17.32±6.3	19.58±8.36	NS

* – significant differences between the 1st and 2nd or 3rd trimester; # – significant differences between the controls and pregnant women in the 1st trimester; & – significant differences between the controls and pregnant women in the 3rd trimester. E/I ratio – mean ratio of the longest RR interval during expiration to the shortest RR interval during inspiration counted from 6 consecutive cycles. ΔI–E – the difference between maximal heart rate during inspiration and minimal during expiration, DBD – the deep breath difference, RSA – respiratory arrhythmia index, HR – heart rate, BPs – systolic blood pressure, BPd – diastolic blood pressure, VR – Valsalva ratio – the ratio of the R-R interval between the longest R-R interval during the test and the shortest R-R interval after the test, *p* – level of statistical significance. Data are presented as mean arithmetical values ± SD.

(1994); however, these authors did not analyze the changes of TFC in other trimesters.

Circulatory baroreflexes constitute important mechanism involved in the maintenance of the blood pressure and flow. However, the results of previous studies of baroreflex function in pregnant woman are inconclusive, as all increased, unchanged, or decreased cardiovagal baroreflex sensitivity (BRS) has been reported (Rang *et al.* 2002; Faber *et al.* 2004; Voss *et al.* 2000). These discrepancies may result from methodological differences between previous studies and/or differences in analyzed stages of gestation. In contrast, the results of numerous studies regarding cardiovagal baroreflex dysfunction in gestational hypertension and preeclampsia are relatively consistent in documenting impaired baroreflex function. Our study of healthy women revealed a decrease in BRS in the 2nd and 3rd trimester. The marked sympathetic activation during the third trimester of gestation, documented in both our and previous studies, points to inhibitory restraint of central sympathetic outflow as one potential cause of BRS fall (Faber *et al.* 2004).

While cardiac vagal activity is decreased in normal pregnancy, the sympathetic activity is increased in late gestation. Therefore, autonomic nervous activity seems to be shifted towards a lower sympathetic and higher vagal modulation in the first trimester, and towards a higher sympathetic and lower vagal modulation later in the pregnancy (Ekholm & Erkkola 1996; Ekholm *et al.* 1997; Kuo *et al.* 2000; Voss *et al.* 2000). This is consistent with our findings on autonomic response to stimuli, as HRV parameters documented in our study corresponded to a gradual decrease in response to both sympathetic and parasympathetic stimulation.

The respiratory fluctuations in the heart rate are likely to be primarily mediated by parasympathetic efferent pathways. Loss of the normal respiratory sinus arrhythmia is often the earliest sign of autonomic neuropathy in diabetes mellitus [20]. Inspiration and expiration at a constant rate accentuate the normal respiratory sinus arrhythmia observed in most individuals (Ekholm & Erkkola 1996; Rang *et al.* 2002; Lahiri *et al.* 2008). Our study documented a decrease in E/I ratio, ΔI–E, DBD, and RSA in response to both DB test and Valsalva maneuver (VM) performed in the 3rd trimester. These results are consistent with data reported by Souma *et al.* (1983), who demonstrated a downward trend in the Valsalva ratio of pregnant women up to the 32nd week of gestation. This suggests that blunted response to both stimuli may result from a progressive decrease in the vagal activity of pregnant women.

The pressor response is strongly correlated with an increase in muscle sympathetic neural activity, as shown by direct recording of the latter (Rang *et al.* 2002). Our findings are consistent with the results published by Greenwood and Avery (Greenwood *et al.* 1998; 2003; Avery & Wolfe 2001), who observed weaker response of pregnant women to sympathetic stimulation during orthostatic stress or exercise (Avery & Wolfe 2001). We showed a decrease in CPT-provoked diastolic LF-dBPV and HF-dBPV, and systolic LF-sBPV and HF-sBPV between the 1st and 3rd trimester, along with an increase in LF/HF-dBPV and LF/HF-BPV ratios. Also the indices of CPT, Δ sBP, Δ dBP, and Δ HR, decreased between the 1st and 3rd trimester. These changes suggest a down regulation of adrenergic receptors resulting from prolonged sympathetic stimulation, thus explaining the blunted transduction of sympathetic impulse into vascular resistance during pregnancy.

CONCLUSIONS

Maternal cardiovascular adaptation to pregnancy involves dramatic changes in the activity of ANS. Those changes follow characteristic pattern. An increase in HR and BP results from central sympathetic outflow with decreased baroreceptor inhibition. Our findings suggest that hypervolemia, which is caused by the creation of additional placental circulation and limited distribution of blood to several areas, and by the activation both sympathetic and RAS systems, constitutes the primary trigger of the autonomic and hemodynamic changes.

In conclusion, combined measurement and estimation of cardiovascular and autonomic system activity parameters are vital for understanding the physiology and pathophysiology of cardiovascular adaptations in pregnant women, and for recognizing early pathophysiologic changes that may disturb development of gestation.

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Conflicts of interest

The authors declare no conflicts of interest.

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