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DYSAUTONOMIA INVOLVEMENT IN MATERNAL CARDIAC ARRHYTHMIA

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Abstract

Introduction. The role of autonomic imbalance in maternal cardiac arrhythmia (CA) is still debatable.
The objective of the study was to assess the relationship between maternal autonomic tone and CA in pregnant women.
Materials and methods. The cross-sectional study was carried out among pregnant women admitted to Kharkiv Municipal Perinatal Center between 1 December 2015 and 31 July 2020. 117 patients at 28-36 weeks of gestation were enrolled. 20 of them had sinus rhythm and were included in Group I (control). In Group II, 55 pregnant women with CA and cardiovascular comorbidity were observed. 42 patients with idiopathic CA were monitored in Group III. The daily electrocardiogram and heart rate variability (HRV) were obtained. The density of ectopic beats (DEB) was defined as the percentage of ectopic to total beats.
Results. The investigation of the HRV revealed heterogeneity in the groups of study. The enhanced sympathetic activity was determined in women with CA and structural heart disease. Pregnant women with idiopathic CA demonstrated a parasympathetic pattern of

Résumé

Implication de la dysautonomie dans l'arythmie cardiaque maternelle

Introduction. Le rôle du déséquilibre autonome dans l'arythmie cardiaque maternelle (AC) est encore discutable.
L'objectif de l'étude était d'évaluer la relation entre le tonus autonome maternel et l'AC chez les femmes enceintes.
Résultats. L'enquête de la DEB a révélé une hétérogénéité dans les groupes d'étude. L'activité sympathique accrue a été déterminée chez les femmes atteintes d'AC et de cardiopathie structurelle. Les femmes enceintes atteintes d'AC idiopathique ont démontré un schéma parasympathique de régulation nerveuse autonome. Les relations révélées entre DEB et la régulation sympathique ou parasympathique démontrent une augmentation du tonus sympathique chez les patients atteints de cardiopathie structurelle. Chez les femmes atteintes d'AC idiopathique, la régulation parasympathique a joué un rôle important dans le scénario de l'ectopie cardiaque.

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autonomic nervous regulation. The revealed relations between DEB and sympathetic or parasympathetic regulation demonstrate an increased sympathetic tone in patients with structural heart disease. In women with idiopathic CA, parasympathetic regulation played a significant role in the scenario of cardiac ectopy.
Conclusions. The idiopathic CA could be the result of abnormally elevated parasympathetic regulation in the second half of pregnancy.

Keywords: maternal arrhythmia, structural heart disease, heart rate variability, autonomic malfunction.

List of abbreviations.
CA – cardiac arrhythmia
HRV – heart rate variability
DEB – density of ectopic beats
ECG – electrocardiogram
AC – acceleration capacity
DC – deceleration capacity
LV – left ventricle
EchoCG – echocardiography
MV – mitral valve
LF – low frequency
HF – high frequency
SDNN – the standard deviation of normal-to-normal intervals
VLF – very low frequency

Conclusions. L'AC idiopathique pourrait être le résultat d'une régulation parasympathique anormalement élevée dans la seconde moitié de la grossesse.

Mots-clés: arythmie maternelle, cardiopathie structurelle, variabilité de la fréquence cardiaque, dysfonctionnement autonome.

Introduction

The autonomic modulations during gestation are known to be involved in the scenario of a healthy pregnancy. The increased parasympathetic regulation could be a trigger of gestational hypervolemia and decreased peripheral vascular tone in the process of fetal growth and maturation[1,2]. Pre-eclampsia is associated with an enhanced sympathetic tone, reduced vagal activity, and a hypokinetic type of maternal hemodynamics in severe cases. This gestational disease is known to be featured by general vasoconstriction and arterial hypertension[3,4]. Therefore, an autonomic imbalance could be a sign of cardiovascular disorders in pregnant women.

The ectopic atrial or ventricular beats are frequent findings on electrocardiograms (ECG) in pregnant women. These arrhythmic events could be silent or have some clinical signs. Sometimes, cardiac arrhythmia (CA) is related to structural heart disease, but it also could be detected without any comorbidity[5-7]. The autonomic involvement in the scenario of ectopic beats is still an issue.

The objective of the study was to assess the relationship between maternal autonomic tone and CA in pregnant women.

Materials and methods

The ethical approval of the study protocol was received from the Research Council and the Ethical Committee of the Kharkiv Medical Academy of Postgraduate Education, no 11.1019p (15. 10.2015). The patients signed an informed consent to participate. 117 patients at 28-36 weeks of gestation were enrolled in the study. Criteria for inclusion: singleton pregnancy, cardiac ectopy, structural heart disease. Exclusion criteria: any gestational pathology, including pre-eclampsia, threatened preterm labor, fetal growth restriction, chronic arterial hypertension, and any hepatic, kidney, or endocrine diseases, etc. The prospective cross-sectional study was carried out among pregnant women admitted to Kharkiv Municipal Perinatal Center between 1 December 2015 and 31 July 2020.

Cardiac rhythm disturbances were detected in 97 women. 20 of them had sinus rhythm and were included in Group I (control). In Group II, 55 pregnant women with CA and cardiovascular comorbidity were observed. 42 patients with idiopathic CA were monitored in Group III.

The daily maternal ECG and heart rate variability (HRV) parameters were obtained with electrocardiographic equipment "Cardiosens" (Scientific Research Center "KhAI-Medica", Ukraine). The number of ectopic beats (>10 per hour) was calculated. The density of ectopic beats (DEB) was defined as the percentage of ectopic to total beats. The conventional linear and non-linear parameters of HRV were investigated[7]. The acceleration capacity (AC) and the deceleration capacity (DC) were also determined through the phase-rectified signal averaging technique[8]. The variables of HRV were calculated from the tracing without ectopic beats, typically, before the onset of the attack.

Structural and functional parameters of the left ventricle (LV) were assessed using Doppler echocardiography (EchoCG) with the ultrasound scanner "Vivid 3" (Japan) and a 3.5 MHz probe in a prone position on the left side from the parasternal and apical four-chamber views. The following indices of EchoCG were assessed: aortic diameter, aortic, mitral valve (MV), tricuspid valve opening amplitude, the whole area of all these valves[9]. The morphometry and function of mitral valve were performed in M-mode in the standard position II; in the mode of two-dimensional EchoCG – in the parasternal projection of the LV long axis and the LV transverse axis at the level of the mitral valve, and in the apical four-chamber position. All ultrasonographic examinations were performed by a single specialist.

The Statistical Package for Social Sciences (SPSS) program (SPSS for Windows, Version 25.0, Chicago, IC, USA) was used for statistical analysis. The results were presented as mean and standard deviations for numerical variables, and frequencies and percentages for categorical data. The suitability of numerical variables to normal distribution was evaluated using skewness values and histograms.

The independent sample t-test was used in comparing numerical variables fitting a normal distribution. Variables that did not conform to normal distribution were analysed by the Mann-Whitney U test. The Chi-Square (or Fisher's exact) test was used for comparing categorical variables. Spearman correlation analysis was used to assess the relationships between numerical variables. A p-value of <0.05 was considered sufficient for statistical significance.

Results

40 (34. %) women from the group with ectopic beats were smokers. Most of them, 65 persons (55.6 %) had a family history of cardiovascular diseases. Palpitations, dizziness, chest discomfort, and anxiety were found in patients with CA and heart disease (Group II). Most of the patients in Group III were asymptomatic.

EchoCG showed that the sign of mitral valve prolapse was the displacement of the valve (s) to the left atrial cavity by more than 3 mm. The systolic deflection of one or both valves of the MV in the left atrium by 3.0 – 5.9 mm, in the parasternal longitudinal position, is defined as first degree MV prolapse, by 6-8.9 mm – second degree MV prolapse and by more than 9 mm – third degree. The normal values of the anterior MV cusp length were 21-24 mm, and of the posterior one 12-14 mm. The MV prolapse was detected via ultrasound in 38 women from Group II. The mitral regurgitation of first degree was found in 6 patients, and of second degree in 32 pregnant women. Rheumatic mitral insufficiency was diagnosed in 5 women, post-myocarditis cardiosclerosis in 11 patients, and patent oval foramen in one case.

The DEB, detected via daily Holter ECG monitoring, was found 26.0% higher ($p<0.05$) in Group II than in Group III, and 7.6 times higher than in Group I. The DEB of atrial or junctional origin in women with structural heart disease was 2.8 and 7.0 times higher than in Group III, and Group I ($p<0.05$), respectively. The DEB of ventricular premature contractions was 2.5 times higher than supraventricular ectopic beats in the case of MV prolapse ($p<0.05$). The DEB of ventricular premature contractions was almost similar in Group II and Group III.

The investigation of the HRV variables revealed heterogeneity in the groups of study (Fig. 1, 2). The maximal level of the autonomic regulation with a stable sympathovagal balance was found in Group I. The activity of sympathetic and parasympathetic tones was almost equal according to the power spectrum in low frequency (LF) and high frequency (HF) domain regions. The values of the sympathovagal (autonomic) balance were: 1.0±0.2 c.u.; 2.1±0.4 c.u.; and 0.84±1.1 c.u., respectively, in Group I, Group II, and Group III ($p<0.05$). The decreased linear and non-linear parameters of the autonomic tone (standard deviation of normal-to-normal intervals (SDNN) and total power (TP)) were detected in Group II (Fig. 1, 2). The enhanced sympathetic activity through elevated LF, mode amplitude (AMo), and stress index (SI) was determined in women with CA and structural heart disease. The reduced variables of parasympathetic regulation (the root mean square of successive heartbeat interval differences (RMSSD) and HF) were found. The values of AC were: – 20.8±5.4 ms; – 6.1±6.3 ms; and –18.8±5.1 ms, respectively in Group I, Group II, and Group III ($p<0.05$). The values of DC were also different: 18.5±4.8 ms; 14.6±5.2 ms; and 17.1±4.3 ms, respectively in Group I, Group II, and Group III ($p<0.05$). The changes in AC/DC capacity supported

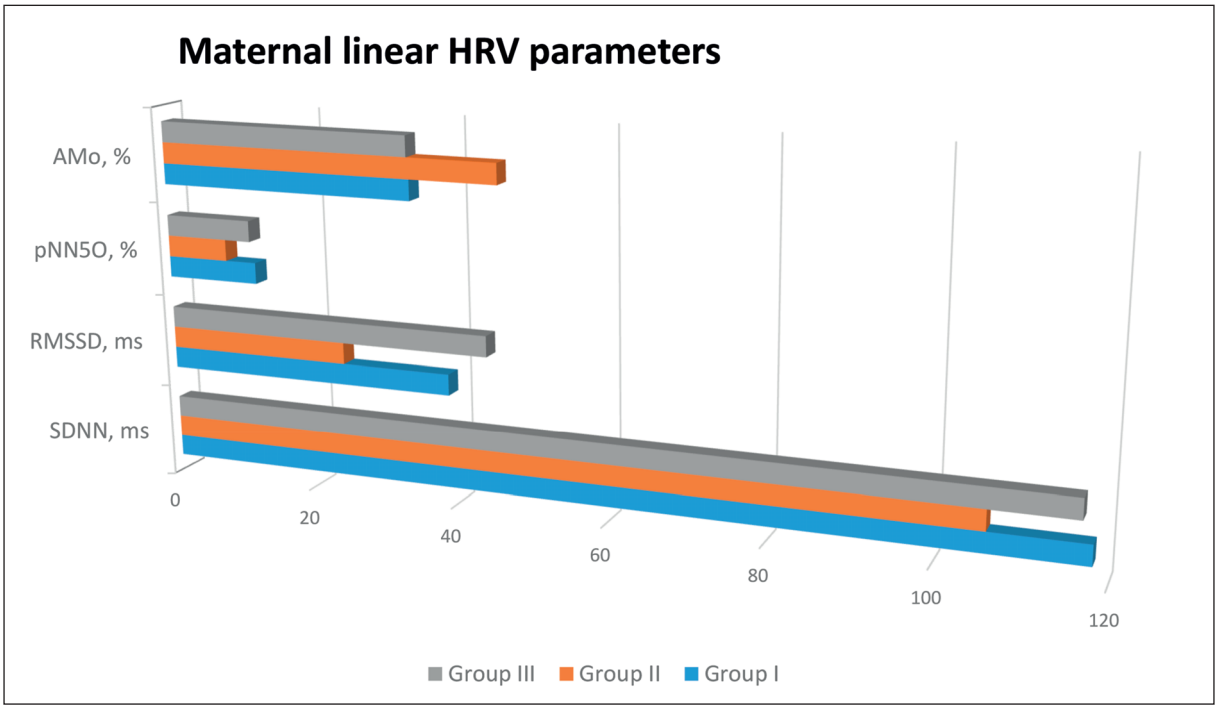

Figure 1. Maternal HRV parameters in the study population.
Abbreviations: SDNN – the standard deviation of normal-to-normal intervals;
RMSSD – the root mean square of successive heartbeat interval differences;
pNN50 – the proportion of NN pairs differing by more than 50 ms divided by total number of NNs;
AMo – the mode amplitude (the most frequent value of NN interval or the highest column in the histogramm) –
the number of NN intervals included into the pocket corresponding to the mode measured in percentages (%) (AMo).

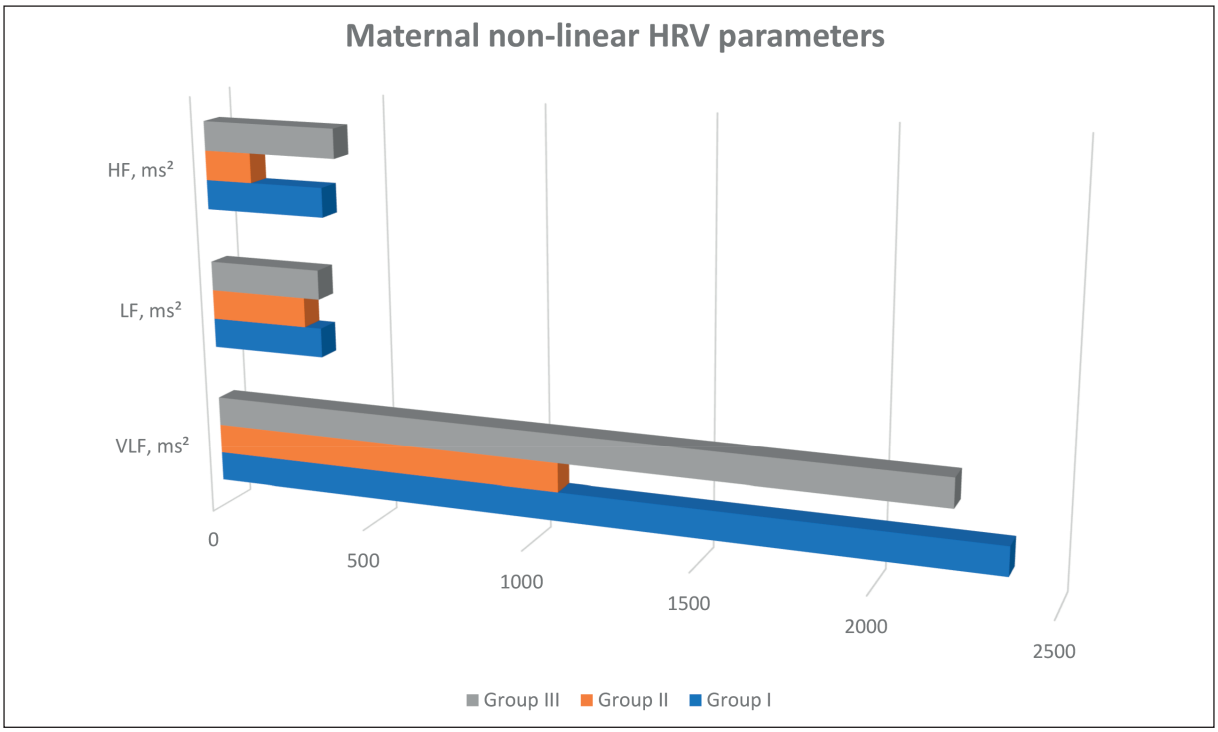

Figure 2. Maternal non-linear HRV parameters in the study population.
Abbreviations: VLF – the very low frequency; LF – the low frequency; HF – the high frequency.

Table 1. Spearman's correlations between the TP and DEB, the LF and DEB, the HF and DEB in the study population.

Pairs of parameters (X versus Y)	*Group II*	*Group III*
TP vs DEB	R=-0.45*	R=0.12
LF vs DEB	R=0.60*	R=0.14
HF vs DEB	R=0.10	R=0.62*

* – the correlation was statistically significant ($p<0.05$)

the sympathetic overactivity in women with CA and structural heart disease. The safety of the autonomic tone was detected in Group III. The power of regulation in the HF domain region and RMSSD were elevated. Therefore, pregnant women with idiopathic CA demonstrated a parasympathetic pattern of autonomic nervous regulation. The values of the AC/DC reflected the stability of gestational autonomic modulations.

The variables of Spearman`s correlation in pairs: TP vs DEB, LF vs DEB, and HF vs DEB showed some regularities (Table 1). A moderate negative correlation was detected between TP and DEB in Group II, and a strong positive correlation between LF and DEB was found. A strong positive relationship in pair HF vs DB was determined. Thus, the different autonomic involvement could be suspected in pregnant women with CA.

Discussion

The role of autonomic imbalance in the pathogenic scenario of pre-eclampsia is already known[2,3]. This gestational disease has a negative influence on the cardiovascular system even after the cessation of pregnancy. Our research makes an emphasis on dysautonomia in the development of cardiovascular disease.

We have found the different autonomic modulations in pregnant women with CA. The revealed relations between DEB and sympathetic or parasympathetic regulation demonstrate the different origins of CA in pregnant women. Since the parasympathetic part of autonomic nervous regulation was found dominant in a healthy pregnancy, the absence of the regulatory resetting in patients with CA and structural heart disease was revealed[10]. The elevated sympathetic tone decreased total autonomic regulation. The revealed features were found to contribute to the development of hypovolemia, vasoconstriction, increased vascular permeability, and superimposed pre-eclampsia[2-4,11]. MV prolapse is a sign of connective tissue dysplasia[12,13]. This disorder is associated with sympatheticonia, thrombophilia, and systemic inflammation[14,15]. Other cardiac disorders found in Group II had an inflammatory mechanism of development. An increased sympathetic tone captures elevated pro-inflammatory activity[16-18].

Following the fetal programming hypothesis, cardiovascular disease has its origin in the antenatal period of life[19]. Fetal compromise is associated with increased sympathetic regulation and delayed neurological development[20]. Probably, an autonomic malfunction has its projection on cardiovascular health in the future. Maternal hypertensive disorders during pregnancy could be a trigger for cardiovascular disease[21]. The role of neuroinflammation was hypothesized in the development of disturbed autonomic regulation[11]. Thus, autonomic imbalance and reduced HRV are the well-known pathogenic links to atherosclerosis and coronary heart disease[22,23].

In women with idiopathic CA, the parasympathetic regulation played a significant role in the scenario of cardiac ectopy[24,25]. Thus, this peculiarity should be considered, to avoid the use of β-blockers in case of decreased (less than 1) sympathovagal balance. Maternal HRV monitoring is a useful method for the detection of autonomic imbalance in pregnant women with CA[26-28]. We speculate that idiopathic CA in pregnancy could be a result of persistence of increased vagal activity from the first part of gestation. Further investigations are necessary for definite conclusions.

Limitations of the study: the possible check of the findings in a larger population is necessary, to reveal prognostic criteria for pregnancy outcomes in maternal CA and create a strategy for their prevention.

Conclusions

Maternal CA were found to be associated with an increased sympathetic tone in patients with structural heart disease. The idiopathic CA could be a result of abnormally elevated parasympathetic regulation in the second half of pregnancy. Maternal HRV monitoring is necessary to detect autonomic imbalance and to avoid unreasonable prescription of β-blockers.

Author Contributions:

Conceptualization, I.L. and I.K.; methodology, I.L., and O.L.; software, I.K.; validation, K.U. and I.L.; formal analysis, I.L. K. U.; investigation, I. K., I.L. and O. L.; resources, I.K; data curation, I.L. and K.U.; writing–original draft preparation, I.L.; writing–review and editing, I.K, O.L., K.U.; visualization, I.K.; supervision, I.L.; project administration, I.L. All the authors have read and agreed with the final version of the article.

Compliance with Ethics Requirements:

The ethical approval was obtained from Bioethics Committee of the Kharkiv Medical Academy of Postgraduate Education (registration number 0116U002865/15. 10.2015).

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study"

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