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Original Article

The hemodynamic repercussions of the autonomic modulations in growth-restricted fetuses

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ABSTRACT

Objectives: Idiopathic fetal growth restriction is considered to be associated with hemodynamic abnormalities.

Objectives: The study was aimed to the investigation of the relationship between fetal and maternal autonomic balance, arterial and venous hemodynamic Doppler indices and CTG variables in case of normal fetal development and fetal growth restriction.

Methods: 106 patients at 32–40 weeks of gestation were enrolled in the study. 30 of them had healthy pregnancy and were involved in Group I. In Group II, 44 pregnant women with fetal growth restriction and normal umbilical hemodynamic Doppler indices were observed. 32 patients with fetal growth restriction and an absent or reversed end-diastolic umbilical flow were monitored in Group III. The curves of maximum blood flow velocity were isolated and their spectral components were determined from the umbilical Doppler spectrograms. The maternal and fetal heart rate variability, conventional CTG patterns were obtained from RR-interval time series registered from maternal abdominal wall electrocardiographically.

Results: The increased adrenergic regulation has modulated parasympathetic impact on fetal cardiovascular system. The decreased reactivity was mirrored in low LTV, lack of accelerations and an increased score of decelerations.

Results: The CTG findings were also featured by the revealed correlations demonstrated an obvious relationship between fetal and maternal hemodynamics in healthy pregnancy. It was possible to speculate that a controlling signal of 0.5 Hz has played a significant role in the umbilical venous blood flow. The decreased fetal autonomic tone and the fetal and maternal hemodynamic decoupling were found in growth-retarded fetuses.

Conclusion: Fetal heart rate pattern was influenced by maternal and fetal autonomic tone. Maternal cardiovascular oscillations were reflected in the umbilical circulation in healthy pregnancy Fetal distress was featured by sympathetic overactivity and the reduction of vagal tone. Such autonomic modulations was manifested by the decelerative pattern of CTG and deteriorated umbilical hemodynamics.

1. Introduction

HRV is known as a clinically oriented approach to the investigation of fetal neurodevelopment and maturation.[1–4] The concept of the intrauterine programming of the diseases determines a non-invasive diagnosing of fetal well-being as a prospect in perinatology. Fetal autonomic tone is found to be involved in the neurobehavioral response to different stationary conditions. Fetal heart rate captures the continual changes of the autonomic (sympatho-vagal) balance. Ultrasonic CTG is a routinely used method for the assessment of the fetal cardiovascular reactivity to the periods of wakefulness, active or calm sleep and fetal compromise.[13] But this method based on the mechanical measurement of the cardiac intervals is not absolutely specific for the diagnosing of fetal distress. The accuracy of the early detection of fetal compromise is not sufficient. The opinion that fetal electronic monitoring has contributed to an abnormally increased cesareans rate was rather

Abbreviations: HRV, heart rate variability; CTG, cardiotocography; FNIECG, fetal non-invasive electrocardiography; FGR, fetal growth restriction; TP, total power; VLF, very low frequency; LF, low frequency; HF, high frequency; SDNN, the standard deviation of normal to normal intervals; RMSSD, the root mean square of successive heartbeat interval differences; pNN50, the proportion of the number of pairs of NNs differing by more than 50 ms divided by the total number of NNs; AMo, the amplitude of mode; SI, the stress index.

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evident.[5] The extremely large complexity of the relations in the system of "mother-placenta-fetus" is known to have a dramatic impact on two main oscillators – maternal and fetal heart.[6–8] FNIECG has a complicated reputation because of low signal-to-noise ratio but provides the ability to obtain fetal cardiac rhythm tracing based on the initial myocardial bioelectrical processes.[2,5] The assessment of the morphological variables of QRS complex, p and T waves is an evident option of FNIECG.[9]

Idiopathic FGR is considered to be associated with the utero-placental and umbilical hemodynamic abnormalities.[1,10] Fetal circulatory modulations were influenced by the autonomic imbalance. The increased sympathetic and decreased parasympathetic regulation was found in FGR.[1,3,11,12] The abnormal neurodevelopment in FGR could be a reason of altered cardiovascular reactivity. Since an elevated vagal tone is known as a sign of fetal maturation the question of possible correlations between fetal autonomic tone and hemodynamic variables becomes a rather relevant issue in growth-restricted fetuses.

The study was aimed to the investigation of the relationship between fetal and maternal autonomic balance, arterial and venous hemodynamic Doppler indices and CTG variables in case of normal fetal development and FGR.

2. Materials and methods

2.1. Patients

This study was cross-sectional. The study protocol was approved by the Bioethics Committee of the Kharkiv Medical Academy of Postgraduate Education.[13] The eligible participants were informed about the methodology of the study, its aims, objectives, indications and eventual complications before inclusion in the study. All patients who met the inclusion criteria gave written informed consent to participate in the investigation. The cases of the idiopathic FGR were determined. Inclusion criteria: FGR according to ultrasonography. The FGR was in diagnosed in case of fetal weight parameters were lower than 10th percentile.[1,3] Exclusion criteria: multiple pregnancy, preexisting medical disorders like diabetes mellitus, metabolic syndrome, cardiac diseases, renal disease, thyrotoxicosis. 106 patients at 32–40 weeks of gestation were enrolled in the study. And 30 of them had healthy pregnancy and were involved in Group I. In Group II, 44 pregnant women with FGR and normal umbilical hemodynamic Doppler indices were observed. 32 patients with FGR and an absent or reversed end-diastolic umbilical flow were monitored in Group III.

2.2. Methods

Doppler ultrasonography was performed on the ultrasound system "Voluson 730" (GE Healthcare, USA). The obtained within 1 min Doppler spectrogram of the venous umbilical blood flow was subjected to further processing. The curves of maximum blood flow velocity were isolated and their spectral components were determined. The spectra were calculated by sampling step $\Delta t = 0.01$ s for a sample of 256 points. The resulting spectrum was obtained by averaging over all samples of this contingent. The maternal HRV, fetal HRV and conventional CTG patterns were obtained from RR-interval time series registered from maternal abdominal wall electrocardiographically. Fetal noninvasive computer electrocardiographic system "Cardiolab Baby Card" (Scientific Research Center "KhAI-Medica", Ukraine) was used in the study. The Ukrainian fetal ECG recordings were included in PhysioNet Database.[13] The registration was carried out over 10 min. Blind source separation, adaptive noise cancellation and Kalman filtering techniques were used to reduce artifact rate. The sampling rate was 1000 Hz. The values TP and its spectral compounds, i.e. the VLF, the LF, the HF and LF/HF ratio or sympatho-vagal balance, were determined. The temporal characteristics of the fetal HRV: the SDNN, RMSSD, pNN50, AMo (the most frequent value of NN interval or the highest column in the histogram) – the number of NN intervals included in the pocket corresponding to the mode measured in percentages (%) and $SI = AMo(\%)/(2 \times Mo \times Var)$; $Var = NNmax - NNmin$; were calculated.[9]

2.3. Statistics

The results thus obtained were analyzed with an ANOVA test to compare data between groups. For the assessment of the difference between non-parametric variables Mann-Whitney test was used. The significance was set at p-value <0.05. For the statistical analysis of relationship between X and Y, the correlations coefficients were estimated with Spearman's test. Microsoft Office 2010 Excel software was used for statistical analysis (Washington, USA).

3. Results

3.1. Clinical characteristics of the study population

The mean age values were different in patients of Group I, Group II and Group III (Table 1). The mean values of the gestational age were not different significantly between all study groups. The body mass index values supported the absence of pre-gestational metabolic syndrome or malnutrition in the study population. The obtained data made an emphasis on the prevalence of pre-eclamptic women with first pregnancy in the Group III. The rate of the threatened preterm labor was low among all patients. The average fetal weight in patients of Group II and Group III was significantly lower than in healthy pregnancy.

3.2. Fetal HRV in FGR

The investigation of the fetal HRV and CTG variables revealed certain regularities (Table 2). The fetal autonomic tone according to obtained values of TP and SDNN was decreased in women in Group II and Group III. The markers of the sympathetic activity: LF, AMo and SI were elevated in growth-retarded fetuses. The parasympathetic tone was decreased based on revealed values of RMSSD, pNN50, HF, STV. The autonomic balance was found to be elevated in FGR. The decreased fetal heart rate reactivity was mirrored in low LTV in Group II and Group III. The CTG findings in FGR were also featured by lower number of accelerations and an increased score of decelerations.

Table 1
Clinical characteristics of the observed women.

Clinical parameter, units of measure	Group I	Group II	Group III
Age, years	23.2 ± 6,4	29.1 ± 7.2*	26.2 ± 5.1*/**
Gestational age, weeks	35.3 ± 3.6	35.4 ± 2.8	35.2 ± 3.2
BMI	25.6 ± 3.3	23.5 ± 4.0*	28.1 ± 5.4*/**
Parity	1.8 ± 0.6	2.1 ± 0.7*	1.1 ± 0.2*/**
Pre-eclampsia or gestational hypertension, number of cases (%)	–	2 (4.5%)	25 (78.1%)
Threatened preterm delivery, number of cases (%)	–	3 (6.8%)	1 (3.1%)
Average fetal weight percentile	54.6 ± 11.9	8.1 ± 1.6*	6.2 ± 2.0*/**

* The differences were statistically significant compared to Group I ($p < 0.05$).
** The differences were statistically significant compared to Group II ($p < 0.05$).

Table 2
Fetal HRV and CTG variables in the study population.

Index, units of measure	Group I	Group II	Group III
SDNN, ms	50.2 ± 7.8	44.6 ± 7.2*	32.4 ± 6.5*/**
RMSSD, ms	22.0 ± 4.3	21.0 ± 3.5*	14.0 ± 2.4*/**
pNN5O, %	8.4 ± 2.0	6.7 ± 1.8*	3.9 ± 0.6*/**
SI, conv. units	142.6 ± 26.1	341.4 ± 56.3*	925.6 ± 223.4*/ **
AMo, %	34.0 ± 14.2	48.3 ± 18.6*	62.7 ± 19.4*/**
TP, ms^2	1489.6 ± 213.8	1126.4 ± 197.3*	486.8 ± 115.4*/**
VLF, ms^2	1128.3 ± 183.2	725.2 ± 88.6*	242.7 ± 49.6*/**
LF, ms^2	262.5 ± 56.1	311.6 ± 68.1*	198.8 ± 30.6*/**
HF, ms^2	98.4 ± 16.3	90.4 ± 12.5*	45.3 ± 11.4*/**
LF/HF	2.7	3.4	4.4
STV, ms	8.5 ± 2.3	7.9 ± 1.8*	3.9 ± 1.2*/**
LTV, ms	37.6 ± 8.2	34.3 ± 7.8*	19.2 ± 6.1*/**
Number of accelerations	3.6 ± 0.8	1.9 ± 0.5*	0.4 ± 0.1*/**
Number of decelerations	0.3 ± 0.1	1.6 ± 0.4*	2.7 ± 0.8*/**

* The differences were statistically significant compared to Group I ($p < 0.05$).
** The differences were statistically significant compared to Group II ($p < 0.05$).

3.3. The revealed correlations

The obvious peak with frequency 0.5 Hz was determined on the curves of blood flow velocities variability. The mean values of the amplitude of 0.5 Hz peak were: 2.1 ± 0.5 c. u., 1.5 ± 0.4 c. u. and 0.4 ± 0.1 c. u. respectively in Group I, Group II and Group III. The force of the correlation between maternal autonomic balance and an amplitude of 0.5 Hz peak among the groups was different (Table 3). The force of the relationship was maximal in Group I. The relations were disturbed in Group II and the Group III. Similar trends were found in the pair fetal autonomic balance vs an amplitude of 0.5 Hz peak. The correlations between the fetal autonomic balance and umbilical artery IR were almost constant in Group I and Group II. The force of correlation was lower in growth-retarded fetuses with abnormal hemodynamic indices. The correlations between the fetal autonomic balance and STV were also almost on the same level both in healthy pregnancy and in FGR with normal hemodynamic indices. The relationship between the fetal autonomic balance and LTV was found to have a moderate force in all study groups. The normal non-stress reactivity was associated with moderate correlation in the pair fetal autonomic balance vs mean number of accelerations in Group I and Group II. The low amount or even absence of accelerations was detected on non-reactive CTG patterns obtained in Group III. The force of correlation between the fetal autonomic balance and the number of decelerations was lower in healthy pregnancy than in FGR.

4. Discussion

The growth of the parasympathetic regulation is a sign of fetal maturation in the last weeks of gestation.[2] Fetal HRV in FGR was lower than in healthy pregnancy. But it was previously found that in case of FGR with normal hemodynamic indices the parasympathetic regulation was safe.[12] The lack of vagal tone was found in distressed fetal status in Group III. The overactivity of the central sympathetic circuit could be involved in the suppression of the autonomic nervous regulation and vagal tone.[12,14] So, the increased adrenergic regulation has modulated parasympathetic impact on fetal cardiovascular system. Fetal hemodynamics captured autonomic modulations. Hypersympatheticotonia was a mainstream in the scenario of fetal compromise. Therefore, fetal autonomic malfunction altered fetal growth and neurological maturation.

Table 3
Statistically significant ($p < 0.05$) Spearman's correlations between fetal TP and other variables in the study population.

Pairs of parameters (X vs Y)	Group I	Group II	Group III
Maternal autonomic balance vs amplitude of the 0.5 Hz peak	R = −0.60	R = −0.42	R = −0.12
Fetal autonomic balance vs maternal autonomic balance	R = 0.64	R = 0.38	R = 0.18
Fetal autonomic balance vs umbilical artery IR	R = 0.52	R = 0.50	R = 0.36
Fetal autonomic balance vs STV	R = −0.54	R = −0.56	R = 0.32
Fetal autonomic balance vs LTV	R = 0.46	R = 0.41	R = 0.48
Fetal autonomic balance vs mean number of accelerations	R = 0.55	R = 0.52	R = 0.25
Fetal autonomic balance vs mean number of decelerations	R = 0.28	R = 0.32	R = 0.44

The peak with a frequency 0.5 Hz was determined in the tracings of the umbilical blood flow velocity variability.[11] This driver had a possible maternal origin. The umbilical vein could be approached as a "mirror" of the oscillatory processes in the "mother-placenta-fetus" system since the cord is not an innervated tissue. Previously, the absence of 0.5 Hz peak was found to be associated with pulsatile flow pattern and low Apgar score.[9] The amplitude of the peak demonstrated a progredient decrease in FGR mostly in case of hemodynamic disturbances. The evident decrease of the amplitude of this peak was possibly involved in the deterioration of the umbilical venous circulation. This peculiarity could reflect the lack of trophotropic reactions of the umbilical hemodynamics in FGR.

The development of the antenatal fetal distress in FGR was associated with a decreased impact of the maternal cardiovascular oscillations. This speculation was supported by similar trends in relations in the pair fetal autonomic balance vs maternal autonomic balance. The growth of the autonomic balance was influenced by a decreased umbilical end-diastolic blood flow. The deficit of the umbilical arterial circulation was found to have an influence on fetal autonomic tone.[10,11] Thus, reflecting a crucial role of the sympathetic regulation in any fetal stationary condition. The fetal response to motile activity captures sympathetic impact on cardiovascular system.[1,3] The relation between fetal autonomic balance and accelerations in FGR with abnormal hemodynamic indices was weaken with fetal distress progression. Therefore, suppression of the autonomic regulation was a satellite of the non-reactive pattern of CTG. Decelerations in the antenatal period were found as one the most evident of CTG criterion of fetal distress.[3] Since the suppression of the vagal tone in decelerative pattern of CTG in case of the fetal acidemia is well-known the force of correlation between fetal autonomic balance and a number of decelerations was higher than in case of normal fetal status.

The revealed correlations demonstrated an obvious relationship between fetal and maternal hemodynamics in healthy pregnancy. It was possible to speculate that a controlling signal of 0.5 Hz played a significant role in the umbilical venous blood flow. The relations between maternal and fetal autonomic tone indices are known.[7] Maternal and fetal cardiac synchrony is based on parasympathetic mechanisms of coupling.[6,8] The decreased fetal autonomic tone and the disturbed fetal and maternal hemodynamic coupling were found in growth-retarded fetuses with abnormal umbilical circulation. The low amplitude of 0.5 Hz peak in FGR was a sign of maternal and fetal hemodynamic dissociation. The suggested approach could be possibly used in future for the prediction of FGR and fetal distress. The used methodology of the study could not allowed to investigate the dynamics of HRV indices in growth-retarded fetuses. The further investigation of the morphological parameters of fetal ECG could contribute to better understanding of cardiac function regulation in FGR.

5. Conclusion

Fetal heart rate pattern was influenced by maternal and fetal autonomic tone. Maternal cardiovascular oscillations were

reflected in the umbilical circulation in healthy pregnancy. Fetal sympathetic tone was involved in the adaptive response to biophysical activity in normal fetal status. Fetal distress was featured by sympathetic overactivity and the reduction of vagal tone. Such autonomic modulations were manifested by the decelerative pattern of CTG and deteriorated umbilical hemodynamics.

Conflict of interest

The author declared that there is no conflict of interest.

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