INTRODUCTION

Fetal growth and maturation critically depends on the placental function and captures all external impact from the maternal organism. Maturation of the autonomic nervous system demonstrates a fetal growing ability to provide hypothalamic and trophoblastic reactions. Any pathological stimulus may disturb fetal well-being. Theory of fetal programming explains how abnormal fetal status could have repercussions in the great number of diseases in a further [1, 2].

Fetal growth restriction (FGR) is a convenient model for the investigation of abnormalities of fetal development [3, 4]. Fetal heart rate variability (HRV) is a well-known approach for the detection of fetal autonomic function [5]. Results of several recent studies showed that variables of fetal HRV in FGR are disturbed [6, 7]. Amplitude of mode (AMo), stress index (SI) use in fetal distress detection was found [8, 9]. AMo is a number of intervals corresponding to the mode value in % to the sample size. AMo and SI reflect the activity of sympathetic regulation [10]. Therefore the delayed maturation of autonomic nervous regulation could be a sensitive marker of FGR [11, 12]. Non-invasive fetal electrocardiography (NI-FECG) is a prospective method for HRV-indicators study. But it has some limitations. The issue of several recent studies showed that variables of fetal HRV in FGR are disturbed [6, 7]. Amplitude of mode (AMo), stress index (SI) use in fetal distress detection was found [8, 9]. AMo is a number of intervals corresponding to the mode value in % to the sample size. AMo and SI reflect the activity of sympathetic regulation [10]. Therefore the delayed maturation of autonomic nervous regulation could be a sensitive marker of FGR [11, 12]. Non-invasive fetal electrocardiography (NI-FECG) is a prospective method for HRV-indices study. But it has some limitations. The issue is a growing layer of vernix caseosa in terms from 29 to 34 weeks. Good quality of NI-FECG tracing was found in the period of neurological maturation (24–28 weeks) [13, 14].

The aim of this study was to detect several patterns of autonomic nervous regulation in FGR complicated by fetal distress or without fetal distress.

MATERIALS AND METHODS

The study protocol was approved by the Bioethics Committee of the Kharkiv Medical Academy of Postgraduate Education (registration number 0116U002865). The eligible participants were informed about the study's methodology, its aims, objectives, indications and eventual complications before enrollment. Patients from the department of maternal-fetal medicine were selected randomly for the cross-sectional study. Totally 64 patients at 26–28 weeks of gestation were enrolled. FGR were detected in 41 women. 23 patients had normal fetal growth and were included in the Group I (control). 20 pregnant women with FGR without fetal distress were observed in Group II. 21 patients with FGR and fetal distress consists Group III.

The FGR was diagnosed if fetal weight parameters were lower than 10th percentile according to ultrasound. The reversed diastolic component in the umbilical artery (UA), absent a-wave in the ductus venosus (DV) and umbilical vein (UV) pulsation pulsations were the features of fetal distress [15–19]. The fetal HRV and conventional CTG patterns were obtained from RR-interval time series registered from maternal abdominal wall via NI-FECG. The equipment “Cardiolab Baby Card” (Scientific Research Center “KhAI-Medica”, Ukraine) was used. Registration was carried out over 30–60 minutes. Total power (TP) and its spectral components i.e. very low frequency (VLF), low frequency (LF), high frequency (HF) and LF/HF ratio or sympatho-vagal balance was determined.

The temporal characteristics of the fetal HRV were calculated: standard deviation of normal to normal intervals (SDNN), root mean square of successive heartbeat interval differences (RMS-SD), proportion of the number of pairs of NNs differing by more than 50 ms divided by the total number of NNs (pNN50), AMo (the most frequent value of NN interval or the highest column in the histogramm) – the number of NN intervals included in the pocket corresponding to the mode measured in percentages (%) and SI = AMo (%) / (2 × Mo × Var); Var = NMax – NMin [2–5].

Obtained fetal RR interval time series was transformed into CTG tracing. The following CTG parameters were determined: short term variation (STV), long term variation (LTV) and the number of accelerations and decelerations.

Results of the study were analyzed with an ANOVA test to compare data between groups. The significance was set at p <0.05. SPSS for Windows Release 19.0 (SPSS Inc. Chicago, Illinois, license No 15G09207000A) software was used for statistical analysis.

RESULTS

Suppression of the total level of HRV with sympathetic overactivity was found in FGR (Table). The reduced vagal activity according to the values of RMS-SD and HF was detected. FGR was featured by a gradual decrease of TP with a maximal elevation of AMo and SI in fetal distress Group. The maximal growth of sympatho-vagal balance was found in Group III. Fetal deterioration was associated with an increased quantity of decelerations, reduced level of accelerations, and decreased of STV and LTV.
We have found that each group of the study population has its own pattern of the autonomic nervous regulation and CTG curve. The samples are located below.

**Case 1.** A pregnant primigravida woman of 22 years was admitted to the Department of Feto-Maternal Medicine of Kharkiv Municipal Perinatal Center at the term of gestation 26 weeks. The prodromes of any maternal diseases before gestation were not found. First trimester biochemical tests were normal. She had mild pre-eclampsia and FGR. Fetal distress was diagnosed via Doppler ultrasound. The reversed diastolic component in the UA, absent a-wave in the DV and UV pulsations were found. The data of NI-FECG demonstrated the suppressed fetal autonomic tone with the decelerative pattern of beat-to-beat variations (an analog of the ultrasound cardiotocography curve) (Fig. 1). The decreased STV (2.6) supported the diagnosed fetal distress. The variables of HRV were abnormal. TP was decreased (92 ms²). SI = 3102 and AMo = 85% were dramatically elevated. The short cervix (15 mm) was still an issue. Besides well-known hemodynamic Doppler findings, presence of decelerations and decreased beat-to-beat variations are the markers of fetal distress [20–24]. But a

**Case 2.** A primigravida woman aged 31 hospitalized to the Delivery Department because of the preterm rupture of fetal membrane at a term of 27 weeks of gestation. She had regular antenatal visits. No maternal diseases were known. The course of antimicrobial therapy and betamethasone (24 mg) was started. FGR and disturbed circulation in uterine arteries and elevated systolic/diastolic ratio were absolutely normal: TP = 825 ms²; SI = 1068.3 ± 152.8; AMo = 65%. The fetal demise occurred the next day. The labour was induced. Woman delivered a dead male baby of 460 g, 28 cm length, 20 cm head circumference, and Apgar score 5. Baby passed to the Neonatal Resuscitation Unit and sent home in 44 days.

**Case 3.** Pregnant woman aged 28 with the uterine scar was hospitalized to the Department of Feto-Maternal Medicine at 26 weeks of gestation. She had a pelvic fracture because of the traffic accident in her anamnesis. The short cervix (15 mm) was found via ultrasound. Obstetric pessary was inserted. Hemodynamic Doppler ultrasound showed the increased vascular resistance in uterine arteries and elevated systolic/diastolic ratio in the middle cerebral artery. The pattern of fetal beat-to-beat variations obtained by NI-FECG was reactive (Fig. 3). HRV parameters were absolutely normal: TP = 825 ms²; SI = 651; AMo = 65%. Unfortunately, a preterm rupture of the fetal membrane occurred at 29 weeks of gestation. Baby of 810 g, 33 cm length, 24 cm head circumference, and Apgar score 5–6 was delivered via caesarean. Baby passed to the Neonatal Resuscitation Unit and sent home in 44 days.

**DISCUSSION**

Management of pregnant women with an early-onset FGR is still an issue. Besides well-known hemodynamic Doppler findings, presence of decelerations and decreased beat-to-beat variations are the markers of fetal distress [20–24]. But a

### Table. Fetal HRV parameters and CTG indices in the study population

<table>
<thead>
<tr>
<th>Index</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN, ms</td>
<td>42.1 ± 6.1</td>
<td>31.6 ± 4.2*</td>
<td>11.5 ± 2.6*</td>
</tr>
<tr>
<td>RMSSD, ms</td>
<td>21.1 ± 2.8</td>
<td>14.5 ± 2.4*</td>
<td>8.0 ± 0.6*</td>
</tr>
<tr>
<td>pNN50, %</td>
<td>4.1 ± 0.5</td>
<td>2.2 ± 0.3*</td>
<td>1.2 ± 0.2*</td>
</tr>
<tr>
<td>AMo, %</td>
<td>38.2 ± 6.0</td>
<td>51.3 ± 8.9*</td>
<td>62.8 ± 5.6*</td>
</tr>
<tr>
<td>SI, c.u.</td>
<td>660.5 ± 81.2</td>
<td>1068.3 ± 152.8*</td>
<td>2825.1 ± 403.5*</td>
</tr>
<tr>
<td>TP, ms²</td>
<td>814.2 ± 125.1</td>
<td>643.7 ± 88.4*</td>
<td>224.5 ± 40.6*</td>
</tr>
<tr>
<td>VLF, ms²</td>
<td>562.7 ± 89.4</td>
<td>401.0 ± 56.3*</td>
<td>117.0 ± 34.2*</td>
</tr>
<tr>
<td>LF, ms²</td>
<td>151.8 ± 44.6</td>
<td>194.7 ± 29.1*</td>
<td>90.1 ± 11.4*</td>
</tr>
<tr>
<td>HF, ms²</td>
<td>100.6 ± 9.4</td>
<td>49.1 ± 8.3*</td>
<td>16.8 ± 3.5*</td>
</tr>
<tr>
<td>LF/HF</td>
<td>1.5</td>
<td>4.0</td>
<td>5.4</td>
</tr>
<tr>
<td>STV, ms</td>
<td>7.5 ± 2.8</td>
<td>6.0 ± 2.2*</td>
<td>4.1 ± 1.6*</td>
</tr>
<tr>
<td>LTV, ms</td>
<td>21.9 ± 7.1</td>
<td>16.1 ± 5.8*</td>
<td>12.6 ± 4.3*</td>
</tr>
<tr>
<td>Number of accelerations</td>
<td>12.5 ± 2.9</td>
<td>9.9 ± 0.8*</td>
<td>1.1 ± 0.3*</td>
</tr>
<tr>
<td>Number of decelerations</td>
<td>1.4 ± 0.3</td>
<td>8.5 ± 2.3*</td>
<td>8.6 ± 2.4*</td>
</tr>
</tbody>
</table>

* differences were statistically significant compared to Group I, p <0.05;
† differences were statistically significant compared to Group II, p <0.05;
The first case demonstrates that fetal autonomic malfunction and heart rate decelerations were the predictors of antenatal fetal death. The persisted decelerations with accelerations were the signs of mild fetal deterioration because of chronic placental insufficiency in the second case. No markers of fetal distress and normal reactivity were found in the third case. Therefore fetal autonomic malfunction could be a result of the persistent neurological immaturity in FGR.

NI-FECG is a prospective method for fetal monitoring besides some methodological problems [25]. Temporal resolution of this method is satisfactory for the investigation of fetal HRV [13–14]. This study shows that the NI-FECG technique could support the diagnosing of fetal distress in FGR by detecting suppressed HRV and abnormal pattern of beat-to-beat variations. TP, AMo, and SI were good predictors of fetal deterioration in this study. The approach based on the monitoring of fetal autonomic maturity in the diagnosing of its well-being should be tested in further studies.

CONCLUSION

The fetal HRV variables and beat-to-beat variations parameters could be the sensitive markers of the neurological maturation and good predictors for fetal deterioration.

REFERENCES/ЛІТЕРАТУРА

DELAYED NEUROLOGICAL MATURATION IS A CAUSE FOR DISTRESS DURING FETAL GROWTH RESTRICTION

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Theory of fetal programming contributes to a better understanding of the relationship of many human diseases with antenatal period pathology. Regulatory impact of nervous system is of great importance. Fetal growth restriction (FGR) is a convenient model for investigation of the abnormalities of fetal neurodevelopment. Fetal heart rate variability is a well-known approach for fetal autonomic function detection.

The aim of the study was to detect several patterns of autonomic nervous regulation in FGR complicated by fetal distress or without fetal distress.

Materials and methods. Totally 64 patients at 26–28 weeks of gestation were enrolled. 23 patients had normal fetal growth and were included in the Group I (control). 20 pregnant women with FGR without fetal distress were observed in Group II. 21 patients with FGR and fetal distress were included in Group III. Fetal heart rate variability and conventional cardiographic patterns were obtained from the RR-interval time series registered from the maternal abdominal wall via non-invasive fetal electrocardiography.

Results. Suppression of the total level of heart rate variability with sympathetic overactivity was found in FGR. The maximal growth of sympathetic balance was found in Group III. Fetal deterioration was associated with an increased quantity of decelerations, reduced level of accelerations, and decreased of short term variations and low term variations. But a decelerative pattern before 26 weeks of gestation was normal. Therefore fetal autonomic malfunction could be a result of persistent neurological immaturity in FGR. The approach based on the monitoring of fetal autonomic maturity in the diagnosing of its well-being should be tested in further studies.

Conclusion. Fetal heart rate variability variables and beat-to-beat variations parameters could be the sensitive markers of neurological maturation and good predictors for fetal deterioration.

Keywords: fetal distress, fetal growth restriction, fetal non-invasive electrophysiography, neurodevelopment.

ЗАМЕДЛЕНЕ РОЗЗРЕВАННЯ НЕРВОВОЇ СИСТЕМИ – ПРИЧИНА ДИСТРЕСУ ПРИ ЗАТРИМЦІ РОСТА ПЛОДА

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Теорія плодового програмування дозволяє пояснити взаємозв'язок багатьох захворювань людини з патологією антенатального періоду. Велике значення має регуляторний вплив з боку нервової системи. Затримка росту плода (ЗРП) є зручною моделлю для дослідження порушень розвитку його нервової системи. Варіабельність серцевого ритму плода – добре відомий підхід для вивчення його вегетативної функції.

Мета дослідження. Встановити декілька типів вегетативної нервової регуляції при ЗРП, ускладнені дистресом або без дистресу плода.

Матеріали і методи. Усюгда було обстежено 64 пацієнток в термінах гестації 26–28 тижнів. У 23 пацієнток було відмічено нормальне зростання плода. Вони були включені до групи I (контроль). У II групі під спостереженням перебувало 20 патогенів із ЗРП без дистресу плода, у III групі – 21 пацієнток із ЗРП та дистресом плода. Варіабельність серцевого ритму плода та кардіотокографічні записи були отримані шляхом обробки тривалості інтервалів RR, зареєстрованих із черевної стінки матері за допомогою неінвазивної електрокардіографії плода.

Результати. Притягнення загального рівня варіабельності серцевого ритму із підвищенням симпатичної активності було виявлено при ЗРП. Максимальне зростання симпатовагального балансу було виявлено у III групі. Погіршення стану плода було пов'язане зі збільшенням кількості дцелераций, зниженням рівнем акцелераций та зменшенням значень короткотривалих та довготривалих коливань частоти серцевих скорочень. Але до 26 тижнів вагітності наявність децелераций є нормальним явищем.

Висновок. Показники варіабельності серцевого ритму плода та параметри «удар до удару» вариаций можуть бути чутливими признаками неврологічного созревання та маркерами погіршення стану плода.

Ключові слова: дистрес плода, затримка росту плода, неінвазивна електрокардіографія плода, розвиток нервової системи.