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REVIEW ARTICLE

Fetal Neurobehavior in Normal and High-Risk Pregnancy

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ABSTRACT

Investigations of the fetal behavior in comparison with morphological studies led to the conclusion that fetal behavioral patterns directly reflect developmental and maturational processes of fetal central nervous system. Four-dimensional (4D) ultrasound has remarkably improved the assessment of the quality of fetal spontaneous movements, and enabled a better evaluation of fetal behavior. Recently, new prenatal screening test for assessment of fetal behavior, based on 4D ultrasound, has been published. We present you review of literature on fetal behavior in normal and high-risk pregnancies, and summarized results of new promising prenatal neurological screening test.

Keywords: Fetal behavior, Four-dimensional ultrasound, Prenatal brain impairment, Fetal neurologic screening.

INTRODUCTION

Fetal behavior could be described as any fetal action observed by the mother or any other more objective method as ultrasonography. Through history, maternal registration of fetal movements and obstetrician auscultation of fetal heartbeats in the previous century were the only methods of the follow-up of fetal well-being *in utero*. A turning point in the assessment of fetal behavior was the development of real time two-dimensional (2D) ultrasound that enabled the direct visualization of fetal anatomy and activity. Investigators started to analyze the dynamics of fetal behavior in comparison with morphological studies, which led to the conclusion that fetal behavioral patterns directly reflect developmental and maturational processes of fetal central nervous system (CNS). Therefore, it was suggested that the assessment of fetal behavior in different periods of gestation may provide the possibility to distinct between normal and abnormal brain development as well as early diagnosis of various structural or functional abnormalities.[1]

According to Prechtl et al, any fetal brain damage will interfere with the endogenous motor activity.[1-5] Therefore, spontaneous movements, as an expression of neural activity, could be used as a marker for fetal brain status.[1,4] Consequently, the observation of the unstimulated fetus should contribute to the assessment of the CNS function.[6-16] The remarkable continuity of endogenously generated activity from prenatal to postnatal life may allow identification of those fetuses and infants with evolving neurological impairment.[1,5,17-20]

FETAL NEUROBEHAVIOR IN NORMAL PREGNANCIES

Although early embryonic development is characterized by the immobility of an embryo, between 7 and 15 weeks of gestation most types of movement pattern will emerge.[21] Based on the first analysis of fetal movements by 2D ultrasonography, de Vries classified movements into different patterns which are as follows:[12,22] Sideways bending, startle, general movements, hiccups, breathing-like movements, isolated arm or leg movement, twitches, clonic movements, isolated retroflexion of the head, isolated rotation of the head, isolated anteflexion of the head, jaw movements, sucking and swallowing, hand-head contact, stretching, yawning and rotation of the fetus. The introduction of four-dimensional (4D) ultrasound brought significant advance in the investigation of fetal behavior by providing the capability of simultaneous spatial imaging of the entire fetus and its movements.[13,21,23-26] First spontaneous fetal movements can be observed with conventional 2D ultrasound around the 8th gestational week, while the 4D ultrasound allows the visualization of fetal motility at 7 weeks of gestation.[21,27,28] Our longitudinal study, performed by the 4D ultrasound in 100 fetuses from all trimesters of normal pregnancies has shown increasing frequency of various movement patterns, such as general movements, isolated arm and leg movements, stretching as well as head movements during the first trimester. Only the startle movement pattern seemed to occur stagnantly in this period of gestation.[14] Using 4D sonography, general movements were found to be the most frequent movement pattern between 9 and 14 weeks of gestation.[29] The second half of pregnancy is characterized by organization of fetal movement patterns and increase in complexity of movements. The periods of fetal quiescence begin to increase, and the rest-activity cycles become recognizable. Hardly any new movement pattern emerges in this period. The number of general body movements, which tends to increase from the 9th week onwards, gradually declines

during the last 10 weeks of the pregnancy.[30-32] It is very important to point out that general movements are characterized by large variation and complexity in the third trimester.[33] Simultaneously, with the decrease in the number of general movements, an increase in facial movements, including opening/closing of the jaw, swallowing and chewing, was observed using 2D sonography between 28 and 38 weeks of gestation. These movements appeared mostly in the periods of absence of generalized movements, and such pattern was considered to be a reflection of the normal neurologic development of the fetus.[30] However, a revolutionary improvement in the study of fetal facial movements came with the development of three-dimensional (3D) and 4D sonography. Our results confirmed the potential of 3D/4D sonography for the investigation of structural and functional development of the fetal face.[16] The incorporation of 3D ultrasound technology into clinical practice has resulted in remarkable progress in visualization and anatomic examination of the fetal face. Because of its curvature and small anatomic details, the fetal face can be visualized and analyzed only to a limited extent with 2D ultrasound,[34] but 3D-US allows spatial reconstruction of the fetal face and simultaneous visualization of all facial structures, such as the fetal nose, eyebrows, mouth and eyelids. Further, 4D ultrasound provided for the first-time an opportunity to evaluate subtle fetal facial expressions. In addition, the application of 4D sonography in the examination of fetal facial movements has revealed the existence of a full range of facial expressions, including smiling, crying and eye-lid movements,[14,35] similar to emotional expressions in adults, in the 2nd and 3rd trimesters. Other facial movements, such as yawning, sucking, swallowing and jaw opening can also be observed in this period by 4D ultrasound. According to Yan et al, mouthing was the most frequent facial movement during early third trimester whereas the least frequent were scowling and sucking.[36] Longitudinal analysis of the frequencies of different facial movements in the 2nd and 3rd trimesters revealed some interesting results. Contrary to the declining trend of head movement and hand movement patterns from the beginning of the second trimester to the end of the third trimester, a constant increase in the frequencies of almost all facial movement patterns was observed during the 2nd trimester. Various types of facial expression patterns displayed a peak frequency at the end of 2nd trimester. During the remainder of pregnancy, decreasing or stagnant incidence of facial expression patterns was noted.[14] Further, in recent study, main challenge was to determine what proportion of fetal movements resembles those seen in preterm and term infants. Fetal movements were recorded by 4D US in 10 term pregnancies, and after birth, neonatal spontaneous motor activity was recorded. Interestingly, authors found no statistically significant differences in either quality or quantity of fetal hand to face movements or fetal facial movements. There were no movements observed in fetal life that were not present in neonatal life, whereas Moro reflex was present only in neonates. This pilot study confirmed the existence of a prenatal-neonatal continuum even in subtle, fine, movements, such as facial mimics.[26]

FETAL NEUROBEHAVIOR IN HIGH-RISK PREGNANCIES

Abnormalities in fetal motor activity may consist of a delayed first emergence of specific movements, quantitative changes, an abnormal quality of movements (i.e. changes in the execution of movements patterns) and an abnormal development of fetal behavioral (or sleep) states.[37] Intrigued by fetal activity, the researchers studied the behavior of fetuses in various pathological conditions. The first study on diabetes-related influence on fetal motoric activity reveled delayed emergence of fetal behavioral patterns. The results showed that there is a delay of 1 to 2 weeks in almost all observed movement patterns emerging in the first 12 weeks of gestation. Only fetal breathing-like movements were observed for the first time at the same gestational age as in the control group.[38] Further, fetal breathing-like movements in relation to other parameters of fetal well-being in the late diabetic pregnancies were studied. Results showed that breathing-like movements in late diabetic pregnancy were not influenced by Braxton Hicks contractions and did not show a clear-cut state-dependency. It was concluded that the (neural) mechanism underlying fetal breathing-like movements differs from that in normal pregnancy.[39] Van Vliet et al showed that the quality and quantity of the growth restricted fetal motility is disturbed. Authors suggest that some aspects of the CNS function are disturbed in growth-retarded fetuses, even in the absence of fetal distress.[40] Results of another study were in accordance with previous findings that growth restricted fetuses show a delay in the integration of behavioral patterns and a lower coincidence of behavioral states. These findings are particularly evident in the fetuses with a severe increase of peripheral vascular resistance (absence of end diastolic flow in descending aorta) suggesting that a delay in the CNS development is present in asymmetrical growth retarded fetuses and that there is a possible relationship of this delay to the degree of peripheral vascular resistance.[41] In addition, in fetuses suffering from intrauterine growth restriction, fetal movements become slower and monotonous, resembling cramps, and their variability in strength and amplitude is reduced. The alterations in amplitude and complexity of movements in these fetuses do not appear to be due to the oligohydramnios. In cases of premature rupture of fetal membranes and a subsequently reduced volume of amniotic fluid, movements occur less frequently, but their complexity resembles that of movements performed in the normal volume of amniotic fluid.[42] First study of fetal behavior using 4D ultrasound showed that the median value of all movement patterns in the normal fetuses differed from fetuses with intrauterine growth restriction (IUGR).[43] Statistical evaluation revealed significant differences in the distribution of the movements among these groups. A tendency that IUGR fetuses have less behavioral activity than normal fetuses was noted in all observed movement patterns.

Correlation reached statistical significance between normal and IUGR fetuses in the third trimester in hand to head, hand to face and head retroflexion. These recent data on IUGR fetuses obtained by 4D sonography are stimulating and might result in a more effective strategy to assess development before birth and may encourage future use of 4D ultrasound for quantitative and qualitative assessment of fetal behavior as possible indicators of the neurological condition in IUGR fetuses.

Further, severe reduction of fetal movements at the 27th week detected by prenatal 2D ultrasound was observed in case of transplacental infection with coxsackie B3, confirmed by molecular techniques. Late onset of fetal akinesia deformation sequence with mild arthrogryposis was the finding at fetal autopsy following interruption of the pregnancy.[44] Study on the effect of *Listeria monocytogenes* on fetal motility showed that presentation of the infection includes premature labor, an influenza-like illness and reduced fetal movements.[45] Also, it was found that the breathing-like movements could be used as a predictor of intra-amniotic infection.[46]

The major problem with the study of fetal behavior is that it is very time-consuming. Nevertheless, there is no other possible means of assessing the function of the CNS *in utero*. It is important to notice that only if normal behavior is well understood, it is possible to identify and perceive abnormal behavior before birth. Further, 2D ultrasound was considered somewhat subjective method because information needs observer interpretation. The latest development of 3D and 4D sonography that overcame some of the limitations of 2D methods enables precise study of fetal and even embryonic activity and behavior.

ASSESSMENT OF FETAL NEUROBEHAVIOR BASED ON 4D ULTRASOUND

During the last decade, 4D sonography has stimulated studies on fetal behavior with more convincing imaging and data than those obtained by conventional ultrasonic and nonultrasonic methods.[47] 4D ultrasound has improved the assessment of the quality of fetal spontaneous movements, and enabled a better evaluation of fetal behavior in comparison with 2D ultrasound.[45-50] Zagreb group has great experience using 4D ultrasound in the assessment of fetal behavior.[8,11,26,51] Relying on our own experiences and experiences of the leading authors in the field of fetal and neonatal neurology, new prenatal screening test for assessment of fetal behavior has been suggested.[52] The test was named after the first author, Kurjak antenatal neurodevelopmental test (KANET). The following parameters have been incorporated in the test: Isolated head anteflexion, overlapping cranial sutures and head circumference, isolated eye blinking, facial alteration, mouth opening (yawning or mouthing), isolated hand and leg movements, hand to face movements, finger movements and thumb position and gestalt perception of general movements (overall perception of the body and limb movements with their qualitative assessment).

To produce the new scoring test, the Zagreb group identified severely brain damaged infants and those with optimal neurological findings by comparing fetal with neonatal findings.[52] The new scoring system was retrospectively applied in a group of 100 low-risk pregnancies. After delivery, postnatal neurological assessment was performed, and all neonates assessed as normal reached a score between 14 and 20, which we assumed to be a score of optimal neurological development. Subsequently, the same scoring system was applied in the group of 120 high-risk pregnancies in which, based on postnatal neurological findings, three subgroups of newborns were found: Normal, mildly or moderately abnormal and abnormal. Normal neonates had a prenatal score between 14 and 20, mildly or moderately abnormal neonates had a prenatal score of 5 to 13, whereas those infants who were assigned as neurologically abnormal had a prenatal score from 0 to 5. Ten fetuses who were postnatally, according to neurological assessment, described as mildly or moderately abnormal achieved prenatal score of 5 to 13, while another ten fetuses postnatally assigned as neurologically abnormal had a prenatal score from 0 to 5. Among this group, four fetuses had alobar holoprosencephaly, one had severe hypertensive hydrocephaly, one had tanatophoric dysplasia and four fetuses had multiple malformations. These preliminary results demonstrated ability of KANET to identify abnormal behavior in severely neurologically damaged fetuses.

To verify the new scoring test, study has been continued in several collaborative centers (Zagreb, Istanbul, Bucharest and Doha).[53] This multicentric research included 228 fetuses from high-risk pregnancies, of whom 18 had definite abnormal KANET score. Of these 18 pregnancies, five pregnancies were terminated, and six fetuses died *in utero*. Of seven fetuses with abnormal KANET, postnatal neurological assessment by Amiel Tison's method revealed three newborns out of seven fetuses to be abnormal (arthrogryposis, vermis aplasia and neonate of the mother with the previous child with CP), while four were considered normal (ventriculomegaly, preeclampsia, thrombophylia, oligohydramnios). The three very illustrative cases with abnormal KANET scoring were arthrogryposis, vermis aplasia, and the fetus whose previous sibling had verified cerebral palsy. The fetuses in these three cases had especially reduced facial movements, the faces were like mask during repeated scans. Fetuses with vermis aplasia and arthrogryposis had normal cranial sutures but the isolated head flexion was small in range for both cases. Isolated hand movements, hand to face and leg movements were poor in repertoire for all three cases. The finger movements were cramped and invariable in all three cases. The gestalt perception of GMs was also abnormal in these cases. In this study, the behavior of a fetus with acranius was also longitudinally followed.[53] It has been observed that the fetus at 20 weeks of gestation had hypertonic movements with high amplitude and high speed. The movements emerged abruptly with burst-paused patterns, the variability of head movements was missing, without changes of facial expressions. As the gestational age advanced and the motor control was shifting

from lower to upper control center, the movement patterns changed as well. At the gestational age of 32 weeks, the fetus had no facial expressions (mask-like face) and hand movement repertoire was very poor. At 36 weeks, the absence of both the facial expressions and limb movements was observed. In this fetus abnormal behavior patterns, as a result of lack of the appropriate control of the upper cortical centers on the motor activity, were clearly documented. The objective of this multicentric study was to apply the KANET to the fetuses from high-risk pregnancies for neurological disorders and to verify the results of the test by neonatal neurological assessment. The primary outcome was the usefulness of new antenatal screening test to identify the fetuses from high-risk pregnancies at neurological risk.[53]

Another study confirmed statistically significant difference in fetal behavioral patterns between the fetuses from low-risk and high-risk pregnancies.[54] Statistically significant difference for eight out of 10 parameters of KANET has been showed: Isolated anteflexion of the head, eye blinking, facial expressions (grimacing, tongue expulsion), mouth movements (mouthing, jawing, swallowing), isolated hand movement, hand to face movement, fist and finger movements, and GMs. Statistically significant, moderate correlation of KANET and ATNAT tests was also confirmed. In practical sense, it means that the neuropediatricians who examined the newborns with ATNAT test confirmed the results of KANET.[54]

New results regarding the potential of 4D sonography in the assessment of fetal behavior in high-risk pregnancies were recently published.[55] Up to now, this was the study with the largest number of fetuses (620 fetuses) where prenatal KANET test was applied. Study demonstrated potential of the KANET to detect and discriminate normal from borderline, and abnormal fetal behavior in normal and in high-risk pregnancies.

Above described results of KANET indicate that KANET could become a valuable diagnostic tool for fetal neurological assessment.[52-57] However, further studies in a large population are needed before recommending the use of the test in the routine clinical practice. It is planned to simplify and shorter the duration of the test. Further, sensitivity, specificity, negative and positive predictive value, intraobserver and interobserver reproducibility should also be investigated.

CONCLUSION

In the last three decades, there were several attempts to create a diagnostic test for evaluation of fetal behavior. The tests were different, but none of them were implemented into daily practice.[58-61] KANET is the first prenatal neurological screening test based on the 4D ultrasound technique, whose preliminary results are encouraging.[52-57] At this stage, it seems that KANET separates serious structural anomalies associated with brain impairment. It is our aim to evaluate whether KANET has the potential for antenatal detection of serious neurological problems of other etiologies as well. Although promising, KANET's concept and diagnostic value in the assessment of integrity of the fetal central nervous system needs to be confirmed by studies that are in progress in several world university centers.

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