10.5005/jp-journals-10009-1182

REVIEW ARTICLE

Fetal Brain Function: Lessons Learned and Future Challenges of 4D Sonography

[1]Asim Kurjak, [2]Maja Predojevic, [3]Aida Salihagic Kadic

[1]Professor, Department of Obstetrics and Gynecology, Medical School University of Zagreb, Croatia

[2]Department of Physiology, Medical School University of Zagreb, Croatia

[3]Professor, Department of Physiology, Croatian Institute for Brain Research Medical School University of Zagreb, Croatia

Correspondence: Maja Predojevic, Department of Physiology, Medical School University of Zagreb, Salata 3, 10000 Zagreb Croatia, Phone: 0038514566762, Fax: 0038514590207, e-mail: predojevic.maja@gmail.com

ABSTRACT

Maturation of the central nervous system (CNS) is reflected in fetal behavior. Modern technology, such as four-dimensional (4D) sonography improved assessment of fetal behavior in all three trimesters of pregnancy. After summing 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. Test was named Kurjak antenatal neurodevelopmental test (KANET). Up to now results of KANET are encouraging and they have been published in several prominent journals. Nevertheless, potential of KANET 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.

Keywords: Fetal brain development, Four-dimensional ultrasound, Neurological deficit, Perinatal neurological assessment.

PRENATAL MORPHOLOGICAL AND FUNCTIONAL DEVELOPMENT OF THE FETAL CENTRAL NERVOUS SYSTEM

Development of the human central nervous system (CNS) begins in the early embryonic period and proceeds through a sequence of very complicated processes long after delivery. Early embryonic development is characterized by its immobility. Important prerequisite for fetal movements is the existence of the interneuronal and neuromuscular connections. The earliest interneuronal connections, the synapses, can be detected in the spinal cord shortly before the onset of embryonic motility, at 6 to 7 weeks of gestation.[1] Therefore, the neural activity leading to the first detectable movements is considered to originate from the spinal motoneurons.[2] As mentioned, another important prerequisite for the motility is the development and innervation of muscle fibers. It is well known that primitive muscle fibers (myotubes) are able to contract as soon as they are innervated by motor neurons.[3] Between 6 and 8 weeks of gestation, muscle fibers have formed by fusion of myoblasts, efferent and afferent neuromuscular connections have developed, and spontaneous neural activity causing motility can begin. The first spontaneous embryonic movements are gross body movements and they can be observed at the 7 to 7.5th week of gestation. They consist of slow flexion and extension of the fetal trunk, accompanied by the passive displacement of arms and legs. These so-called vermicular movements appear in irregular sequences. Simultaneously with the onset of spontaneous movements, at the 7.5th week of gestation, the earliest motor reflex activity can be observed, indicating the existence of the first afferent-efferent circuits in the spinal cord. The first reflex movements are massive and indicate a limited number of synapses in a reflex pathway. General movements are the first complex, well-organized movement pattern, which involve head, trunk and limb movements. This pattern has been interpreted as the first sign of a supraspinal control on motor activity and can be recognized from 8 to 9 weeks of gestation onwards.[4]

The brainstem is fashioned around the 7th week of gestation and basic structures of the diencephalon and cerebral hemispheres are formed by the end of the 8th gestational week. The remarkable expansion of the cerebral hemispheres follows during the remainder of gestation. The development of synapses in the human cerebral cortex begins after the formation of the cortical plate, at the end of the 10th week of gestation.[4] The brainstem consists of the medulla oblongata, pons and midbrain. It forms and matures in a caudal to rostral direction. That means the fillogenetically older structures, such as the medulla oblongata, will form and mature earlier in the gestation. In addition to its many subnuclei, the medulla gives rise to a variety of descending spinal motor tracts which reflexively trigger limb and body movements. It also hosts the five cranial nerves (VIII–XII) which exert tremendous influences on gross body movements, heart rate, respiration and the head turning. As the medulla matures in advance of more rostral structures of the brainstem, reflexive movements of the head, body, extremities as well as breathing movements and alterations in heart rate, appear in advance of other functions. The formation of pons begins almost simultaneously but its maturation is more prolonged. The structures of the pons include the V-VIII cranial nerves (vestibular nuclei of the nerve VIII) and the medial longitudinal fasciculus (MLF), pontine tegmentum, raphe nucleus and locus coeruleus, which exert widespread influences on arousal, including the sleep-wake cycles. Facial movements, which are also controlled by V and VII cranial nerve, appear around 10 to 11 weeks.[5] The brainstem gradually begins to take the control over fetal movements and behavioral patterns during the first trimester and continues its maturation in the second trimester, resulting in expansion and complexity of the behavioral repertoires. It should be emphasized that until delivery, subunits of the brainstem remain the main regulators of all fetal behavioral patterns.[5] From 10 weeks onwards, the number and frequency of fetal movements increase and the repertoire of movements begins to expand. Qualitative changes in general movements can also be observed.[6] Using four-dimensional (4D) sonography, we have found that from 13 gestational weeks onwards, a goal orientation of hand movements appears and a target point can be recognized for each hand movement. According to the spatial orientation, they classified the hand movements into several subtypes: hand to head, hand to mouth, hand near mouth, hand to face, hand near face, hand to eye and hand to ear.[7] Our recent longitudinal study, performed by 4D ultrasound in 100 fetuses during 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.[8] Using 4D sonography, general movements were found to be the most frequent movement pattern between 9 and 14 weeks of gestation.[9] From 14 to 19 weeks of gestation, fetuses are highly active and the longest period between movements last only 5 to 6 minutes. In the 15th week, 16 different types of movement can be observed. Besides the general body movements and isolated limb movements, retroflection, anteflection and rotation of the head can easily be seen. Moreover, facial movements, such as mouthing, yawning, hiccups, suckling and swallowing, can be added to the wide repertoire of fetal motor activity in this period.[4] Furthermore, at 16 to 18 weeks of gestation, the earliest eye movements appear as sporadic movements with a limited frequency. The delayed onset of eye movements can be explained with later onset of midbrain maturation. Although the midbrain begins to form at almost the same time as the pons, its maturation does not even begin until the second trimester. It consists of the dopamine producing substantia nigra, the inferior-auditory and superior-visual colliculus, and cranial nerves III-IV, which together with MLF and cranial nerve VI, controls eye movements. Significant trends in fetal eye movement organization can be observed during the second half of pregnancy, especially during the 3rd trimester.[4] Between 15 and 17 gestational weeks, in the zone below the cortical plate, developes a transient fetal structure, subplate zone. Mentioned structure can play a major role in the developmental plasticity following perinatal brain damage.[10] 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.[11-13] Although this decrease was first explained as a consequence of the decrease in amniotic fluid volume, it is now considered to be a result of cerebral maturation processes. As the medulla oblongata matures, myelinates and stabilizes, these spontaneous movements are less easily triggered and begin to be controlled by more stable intrinsic activities generated within the brainstem.[5] It is very important to point out that general movements are characterized by large variation and complexity in the third trimester.[14] 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. 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.[4] However, a revolutionary improvement in the study of fetal facial movements came with the development of 3D and 4D sonography. Our recent studies have found an even wider repertoire of facial and hand movements than it was previously described.[8,15] 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 eyelid movements similar to emotional expressions in adults, in the 2nd and 3rd trimesters. Our longitudinal analysis of the frequencies of different facial movements in the 2nd and 3rd trimester revealed some interesting results.[8] 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, except eye blinking pattern, which displayed a peak frequency at 28 weeks of gestation. During the reminder of pregnancy, decreasing or stagnant incidence of facial expression patterns was noted.[8]

Since the development of the human brain is unique and continuous process that lasts throughout pregnancy and after birth, the continuity of fetal and neonatal movements can be expected as the best indicator of functional brain development.[16] Our recent study has demonstrated that there were no movements observed in fetal life that were not present in neonatal life. Furthermore, prenatal-neonatal continuity exists even in subtle, fine movements, such as facial mimics.[17]

The development of human brain is not completed at the time of delivery. Although neuronal proliferation and migration are completed in a term infant, synaptogenesis and neuronal differentiation continue very intensively. Only subcortical formations and primary cortical areas are well-developed in a newborn. Associative cortex, barely visible in newborn, is scantily developed in a 6-month-old infant. Postnatal formation of synapses in associative cortical areas, which intensifies between the 8th month and the 2nd year of life, precedes the onset of first cognitive functions, such as speech. Following the 2nd year of life, many redundant synapses are eliminated. Elimination of synapses begins very rapidly and continues slowly until puberty, when the same number of synapses as seen in adults is reached.[4]

Understanding morphological and functional development of the central nervous system is important because it could allow identification of the normal and pathological brain development, which could lead to early diagnosis of abnormal brain structure or functional impairment.

NEUROLOGICAL DAMAGE

Intrauterine brain maturation processes take place faster than postnatally. This fact explains why the same hypoxic-ischemic event will have different consequences according to timing: a similar insult will result in a white matter injury at 27 gestational weeks and in a grey matter injury at 39 gestational weeks. Moreover, such hypoxic-ischemic brain damage will have the same result when occurring *in utero* or after birth; in other words hypoxic-ischemic will have identical consequences on the 28 gestational weeks fetus or on the 28th gestational week preterm newborn. In the fetal and neonatal period, white matter injury is more common than injury of the gray matter.[18,19] There is a growing body of evidence that many severe neurological disorders are result of intrauterine rather than postnatal events.[20] Researchers have revealed that neurological disorders, such as minimal cerebral dysfunction, schizophrenia, epilepsy or autism, are at least partly result of prenatal neurodevelopmental impairment.[20,21] Epidemiological studies have shown that even cerebral palsy (CP) is more often caused by prenatal than perinatal and postnatal events.[20]

CP is an umbrella term encompassing a group of motor conditions that cause physical disability due to nonprogressive brain impairment.[22] The diagnosis is retrospective and specificity of the diagnosis improves as the child ages and the nature of the disability progresses. From the pediatric experience diagnosis is rarely set before the age of 6 months, while a definitive diagnosis in most children can be made only after the age of 3 years.[23] This time frame of evolving adverse events should be taken into account when considering the possibility of CP diagnosis in infants.[23] Until recently, it was assumed that CP is associated with trauma during childbirth, prematurity and neonatal hypoxia.[24] Clinical and epidemiological studies have revealed that CP in 70 to 90% of cases results from prenatal rather than intrapartal causes.[25] Isolated intrapartum hypoxia was present in only 4% of severe and moderate neonatal encephalopathy.

The causes of neonatal encephalopathy are heterogeneous and its etiopathogenesis may have origins in preconceptional or antepartal period. In over 70% of cases of neonatal encephalopathy, no evidence of intrapartum hypoxia was found.[25] CP is usually caused by unrecognized, unfavorable events in mid-pregnancy.[24] In some cases, disturbance during pregnancy may reduce fetal physiologic adaptation ability during labor resulting with hypoxic damage.[24]

Optimistic believes, that CP will be completely eliminated, was based on development of modern obstetrics and neonatal care. However, during the past few decades, from 1951, the incidence of CP has remained in general unchanged and ranges from 2 to 4 per 1000 live newborns.[26-28]

NEONATAL NEUROLOGICAL ASSESSMENT

In neonatal neurology there are at least two approaches or schools. French school was founded in the 1950s by Andre Thomas and Saint-Anne Dergassies. They used 'conventional method' based on assessment of muscle tone and reflexes.[29,30] In the 1960s, Claudine Amiel-Tison and Julie Gosselin upgraded this method of neurological examination of the newborn. The second method, introduced by Dutch-Austrian school and initiated and led by Hans Prechtl, was based on monitoring of spontaneous motor activity.[31] This approach advocates a paradigm shift from traditional testing of reflexes and muscle tone towards observation technique of the number and quality of fetal and newborns spontaneous, representing milestone in the functional assessment of the nervous system development.[32]

THE AMIEL-TISON NEUROLOGICAL ASSESSMENT AT TERM

Amiel-Tison has inspired a number of changes in the clinical assessment of the newborn. Neurological assessment at term by Amiel-Tison (ATNAT) is taking into account neurological maturation exploring lower subcortical and upper-cortical systems. The role of lower system is to maintain posture against gravity, while the upper system is responsible for the control of erect posture and for the movements of the extremities. This method involves head circumference measurement, assessment of cranial sutures, visual pursuit, social interaction, sucking reflex, high arched palate, raise-to-sit and reverse, passive tone in the axis, passive tone in the limbs, fingers and thumbs outside the fist and autonomic control during assessment.[33,34] Monitoring the growth of the head and identification of the cranial signs play an important role in the neurological assessment of newborn. During the fetal period and until the age of two years after the birth, the brain volume significantly increases, together with the increase of the head circumference. Sometimes, if brain growth is disturbed, cranial sutures overlap making the ridge. Particularly important is assessment of squamous suture, and presence of the ridge can be an indicator of modest growth restriction of the brain.[35] Passive muscle tone assessment estimates the amplitude of passive movements, for instance, by extension of limb during quiet wakeful state. Passive tone can be hypotonic (normal finding until 28 weeks of gestation) or increased (physiologic finding in the term newborn). In the neonatal period, the extremities are predominantly in the flexed position.[36] Active tone is usually investigated during the traction test, when active movements and control of the head are evaluated. Inspection of child's spontaneous motor activity includes comparison of the limb movements of the left and right side, and assessment of the head position and mobility. Special attention is given to finger movements and thumb position. Thumb should be mostly out of fist, indicating intact upper system of the brain.[36] Observation of the nonreducible adduction of the thumb in a clenched fist is a sign of neurological damage called neurological thumb. During assessment of primitive reflexes special emphasis is given to the sucking reflex. Regular sucking reflex allows proper tongue movement, which promotes growth and development of the hard palate. Other reflexes assessed are: grasp reflex, stepping or walking reflex and Moro reflex . Alertness is estimated by testing the visual fixation and valuing the social interaction. Findings as a weak activity, reduced muscle tension or lethargy may indicate neurological damage.[36] Normal results of the test indicate high probability of favorable neurologic outcome.[36,37] Abnormal finding of described parameters, including neurologic thumb, high-arched palate and overlap of the cranial sutures, may be associated with possible existence of neurological damage.[37]

PRECHTL'S METHOD ON THE QUALITATIVE ASSESSMENT OF GENERAL MOVEMENTS

Prechtl and his followers have defined spontaneous motility as a result complex and active spinal and brainstem machineries, which are subtly modulated by segmental afferent information and ingeniously controlled by supraspinal networks.[32] In other words, the nervous system of neonates displays spontaneous motor patterns that are independent of external stimuli. General movements (GMs) are among the first spontaneous movements human fetus develops. They consist of series of gross movements of variable speed and amplitude, which involve all parts of the body.[32] As already mentioned, GMs motor pattern has been interpreted as the first sign of a supraspinal control on motor activity. GMs are seen in fetuses of 8/9 gestational weeks till 20 weeks post-term. GMs show age-specific characteristics. From 28 to 38 weeks of gestational age spontaneous movements are called premature general movements. These are extremely variable movements, including many pelvic tilts and trunk movements. From 38 weeks to 46-52 weeks, GMs are named writhing movements, they have a tight appearance, a relatively slow speed and a limited amplitude.[18] Writhing movements are replaced with fidgety movements, which consist of an ongoing flow of small, elegant movements, and can be recognized until 58 gestational weeks.[38] Evaluation of GMs is based on the video-recorded movements. Video camera is installed high above the infant who is lying supine in the incubator or bed. Recordings are made while the infant is in state of alertness and last between 30 and 60 minutes in order to collect about three GMs. Later on, recordings are viewed at high speed and GMs are then appraised on a visual gestalt perception of the spatial and temporal variation of motor patterns.[18] GMs can be described as the normal optimal, normal suboptimal, abnormal and definitely abnormal.[14] Abnormal GMs may indicate the presence of neurological damage and particularly important are fidgety movements. It is important to point out that assessment of GMs has a positive predictive value of 89% and negative predictive value of 84% for motor outcome, in very low birth weight infants.[39]

PRENATAL NEUROLOGICAL ASSESSMENT

Motor functions are developed before the speech and cognitive functions, and motor skills assessment is central in evaluation of psychomotor development in the first month of postnatal life. Prenatal motility is considered to reflect the developing nervous system and also involves functional and maturational properties of the fetal hemodynamic and muscular systems. 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 to perceive abnormal behavior before birth. 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 movement patterns) and an abnormal development of fetal behavioral (or sleep) states.[40] Abnormal movement patterns, indicative of altered brain or muscular development, have been described in fetuses with chromosomal anomalies, anencephalic fetuses, fetuses with other cerebral malformations, growth-restricted fetuses and in fetuses suffering from prolonged oligohydramnios.[41] Common features in all these cases are the qualitative changes in the execution of movement patterns, which are abrupt and forceful, with large amplitude in the majority of fetuses with a chromosomal or central nervous system defect and slow, with small amplitude, in the others. Fetal seizures have been described in association with severe brain abnormalities. These movement abnormalities are mainly qualitative and not quantitative in nature, which is in agreement with data on preterm infants with brain lesions.[40,42-44] Recent data on growth restricted fetuses obtained by 4D sonography during the 3rd trimester of pregnancy have shown that growth restricted fetuses have less behavioral activity than normal fetuses in hand to head, hand to face and head retroflexion movements. Statistically significant differences could be shown in the five qualitative categories of head and hand movements.[45] Further, in fetuses suffering from intrauterine growth restriction (IUGR), 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.[44]

The development of 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.[46-49] Zagreb group has great experience using 4D ultrasound in the assessment of fetal behavior.[7,50-52] In addition to the already mentioned studies, in collaboration with Japanese colleagues, two internationally recognized books were recently published.[53,54] After summing 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.[55] The test was named after the first author, Kurjak antenatal neurodevelopmental test (KANET).

KANET evaluates certain movement between 20 and 40 weeks of pregnancy. Selected parameters assessed during application of this new test are: 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, gestalt perception of general movements. Last parameter is defined as overall perception of the body and limb movements with their qualitative assessment (fluency, variability and amplitude). According to the total score, the fetuses are placed to one of the following groups: Abnormal (0-5 points), borderline (6-13 points) and normal (>14 points).

There is a similarity between neonatal optimality test of Amiel-Tison and that new scoring system for the assessment of neurological status in the fetuses. However, analytical criteria of typical passive and active tone in the neonate cannot be elicited in the fetus: head anteflexion versus retroflexion, ventral versus dorsal incurvations in the axis,[35,36] both being of the utmost importance postnatally to confirm CNS optimality.[55] Still, optimality in the fetus should be reflected in typical GMs. In addition to gestalt perception of GMs, leg and head movements are analyzed, parameters that are commonly assessed in the 2D ultrasound studies. The main two advantages of 4D ultrasound in comparison to 2D ultrasound, incorporated in KANET, are the possibility of evaluaton of fetal face movements and better evaluation of the quality of fetal movements. Amiel-Tison has compared the diversity of fetal facial movements with the diversity of fetal facial movements during holding the newborn's head test. In this test, manual support is given to the neck and spine while the infant's alertness and attention are solicited by the examiner: an amazing communication state is reached and facial expression becomes more diversified. The diversity of fetal facial movements could be due to passive support of the fetal head provided by the uterine wall and because of absence of gravity. Amiel-Tison emphasizes the importance of this sign in the assessment of the upper (corticospinal) system.[56] Overlapping of sutures and neurological thumb are included in KANET on suggestion of Amiel-Tison.[56]

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.[55] Ten fetuses who were postnatally, according to neurological assessment, described as mildly or moderately abnormal, achieved prenatal score of 5 to 13, while another 10 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).[57] This multicentric research included 228 fetuses from high-risk pregnancies, of whom 18 had definite abnormal KANET score.[57] 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, pre-eclampsia, thrombophylia, oligohydramnios).[57] 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.[57] In this study, the behavior of a fetus with acranius was also longitudinally followed.[57] 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.[57] In this fetus abnormal behavior patterns, as a result of lack of the appropriate control of the upper cortical centers on the motor activity, was clearly documented.

Another study confirmed statistically significant difference in fetal behavioral patterns between the fetuses from low-risk and high-risk pregnancies.[58] Statistically significant difference for eight out of 10 parameters of KANET has been showed: isolated anteflection 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. Authors have also confirmed statistically significant, moderate correlation of KANET and ATNAT tests. In practical sense, it means that the neuropediatricians who examined the newborns with ATNAT test confirmed the results of KANET.[58]

New results regarding the potential of 4D sonography in the assessment of fetal behavior in high-risk pregnancies were recently published.[59] The group in Khartoum applied KANET to large number of fetuses during the period of one year. The aim of the study was to assess the behavior in large sample of fetuses from normal and high-risk pregnancies by application of the KANET scoring test and to compare the scores obtained in low- and high-risk pregnancies. In this prospective longitudinal cohort study, the KANET was applied in 620 singleton pregnancies, between 26th and 38th week of gestation. There were 520 pregnant women in high-risk and 100 pregnant women in low-risk group. Contrary to the previous studies, the fetuses with congenital anomalies and multiple pregnancies were excluded from the study. High-risk group of patients consisted of the following subgroups: threatened preterm delivery with or without preterm premature rupture of membranes (PPROM), previous child diagnosed with cerebral palsy (CP), hypertension in pregnancy with or without pre-eclampsia, diabetes before pregnancy or gestational diabetes, intrauterine growth restriction, polyhydramnios, Rh isoimmunization, placental bleeding and maternal fever above 39°C. Fetal KANET scores from low-risk and high-risk pregnancies were compared, and the difference was statistically significant.[59] Statistically significant difference was found between KANET scores of the fetuses from the low-risk group compared to the following subgroups of the high-risk group: previous child diagnosed with CP, hypertension (RR > 160/100), threatened preterm delivery, maternal fever, IUGR, Rh isoimmunization, placental bleeding. Furthermore, KANET scores significantly differed comparing threatened preterm delivery with PPROM *vs* threatened preterm delivery without PPROM; hypertension above 160/100 mm Hg *vs* hypertension below 160/100 mm Hg; diabetes before pregnancy *vs* gestational diabetes; IUGR with decreased resistance index (RI) of middle cerebral artery (MCA) *vs* IUGR without decreased RI of MCA; and Rh isoimmunization without hydrops fetalis *vs* Rh isoimmunization with hydrops fetalis. Among the fetuses with abnormal KANET score, most frequently presented were fetuses from the threatened preterm delivery group. Comparison of individual KANET parameters between the fetuses from the low-risk and high-risk pregnancies showed statistically significant difference for overlapping cranial sutures and head circumference, isolated eye blinking, facial expressions (grimacing and tongue expulsion), mouth movements (yawning and mouthing), isolated hand movements, isolated leg movements, hand to face movement, finger movements and GM. For isolated head anteflexion, the difference was not statistically significant.[59] Up to now, this was the study with the largest number of fetuses where prenatal KANET test was applied.

Preliminary results have confirmed the usefulness of KANET in fetal behavior assessment. The KANET test has potential to detect and discriminate normal from borderline and abnormal fetal behavior in normal and in high-risk pregnancies, which means that it could become a valuable diagnostic tool for fetal neurological assessment.[55,57-59] However, further studies in a large population are needed before recommending the use of the test in the routine clinical practice. Also, it seems necessary to simplify the test, may be by grouping some of the parameters, making it more applicable as the screening tool for prenatal neurological assessment. Further sensitivity, specificity, negative and positive predictive values, intraobserver and interobserver reproducibility should also be investigated. KANET is the first prenatal neurological screening test based on the 4D ultrasound technique, whose preliminary results are promising.[55,57-61] Nevertheless, its 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.

REFERENCES

1. Okado N, Kakimi S, Kojima T. Synaptogenesis in the cervical cord of the human embryo: Sequence of synapse formation in a spinal reflex pathway. J Comp Neurol 1979;184(3):491-518.
2. Okado N, Kojima T. Ontogeny of the central nervous system: Neurogenesis, fibre connection, synaptogenesis and myelination in the spinal cord. In: Prechtl HFR (Ed). Continuity of neural function from prenatal to postnatal life. Oxford: Blackwell Science, 1984:31-35.
3. Landmesser LT, Morris DG. The development of functional innervation in the hind limb of the chick embryo. J Physiol (Lond) 1975;249:301-26.
4. Salihagić Kadić A, Predojević M, Kurjak A. Advances in fetal neurophysiology. In: U Pooh RK, Kurjak A (Eds). Fetal neurology. New Delhi: Jaypee Brothers Medical Publishers 2009.
5. Joseph R. Fetal brain and cognitive development. Dev Rev 1999;20:81-98.
6. Lüchinger AB, Hadders-Algra M, VAN Kan CM, DE Vries JI. Fetal onset of general movements. Pediatr Res 2008;63(2): 191-95.
7. Kurjak A, Azumendi G, Vecek N, et al. Fetal hand movements and facial expression in normal pregnancy studied by four-dimensional sonography. J Perinat Med 2003;31:496-508.
8. Kurjak A, Andonotopo W, Hafner T, et al. Normal standards for fetal neurobehavioral developments—longitudinal quantification by four-dimensional sonography. J Perinat Med 2006;34:56-65.
9. Andonotopo W, Medic M, Salihagic-Kadic A, et al. The assessment of fetal behavior in early pregnancy: Comparison between 2D and 4D sonographic scanning. J Perinat Med 2005;33:406-14.
10. Kostovic I, Rakic P. Developmental history of the transient subplate zone in the visual and somatosensory cortex of the macaque monkey and human brain. J Comp Neurol 1990;274:441-70.
11. D'Elia A, Pighetti M, Moccia G, Santangelo N. Spontaneous motor activity in normal fetus. Early Human Dev 2001;65: 139-44.
12. Natale R, Nasello-Paterson C, Turlink R. Longitudinal measurements of fetal breathing, body movements and heart rate accelerations, and decelerations at 24 and 32 weeks of gestation. Am J Obstet Gynecol 1985;151:256-63.

13. Eller DP, Stramm SL, Newman RB. The effect of maternal intravenous glucose administration on fetal activity. Am J Obstet Gynecol 1992;167:1071-74.
14. Hadders-Algra M. Putative neural substrate of normal and abnormal general movements. Neurosci Biobehav Rev 2007;31:1181-90.
15. Kurjak A, Azumendi G, Andonotopo W, Salihagic-Kadic A. Three- and four-dimensional ultrasonography for the structural and functional evaluation of the fetal face. Am J Obstet Gynecol 2007;196:16-28.
16. Stanojevic M, Perlman JM, Andonotopo W, Kurjak A. From fetal to neonatal behavioral status. Ultrasound Review of Obstetrics and Gynecology 2004;4:59-71.
17. Kurjak A, Stanojevic M, Andonotopo W, et al. Behavioral pattern continuity from prenatal to postnatal life—a study by four-dimensional (4D) ultrasonography. J Perinat Med 2004;32:346-53.
18. Amiel-Tison C, Gosselin J. From neonatal to fetal neurology: Some clues for interpreting fetal findings. In: U Pooh RK, Kurjak A (Eds). Fetal neurology. New Delhi: Jaypee Brothers Medical Publishers 2009.
19. Zaputović S, Stanojević M, Mišković B. Od fetalne do neonatalne neurologije. Gynecol Perinatol 2010;19:16-24.
20. Rees S, Harding R. Brain development during fetal life: Influences of the intra-uterine environment. Neursci Lett 2004;361:111-14.
21. Harrison PJ. The neuropathology of schizophrenia: A critical review of the data and their interpretation. Brain 1999;122: 593-624.
22. Stanojević M. Neonatalni aspekt fetalne neurologije. Gynaecol Perinatol 2007;16(suppl 1):10-15.
23. Kurjak A, Pooh RK, Tikvica A, Stanojević M, Mišković B, Ahmed B, Azumendi G. Assessment of fetal neurobehavior by 3D/4D ultrasound. U: Pooh RK, Kurjak A (Eds). Fetal neurology. New Delhi: Jaypee Brothers Medical Publishers 2009.
24. Strijbis EMM, Oudman I, Van Essen P, MacLennan AH. Cerebral palsy and application of the international criteria for acute intrapartum hypoxia. Obstet Gynecol 2006;107:1357-65.
25. Badawi N, Kurniczuk J, Keogh JM. Intrapartum risk factors for newborn encephalopathy: The western australian case-control study. BMJ 1998;317:1554-58.
26. Rosen MG, Diskinson JC. The incidence of cerebral palsy. Am J Obstet Gynecol 1992;167:417-23.
27. Nelson KB. Can we prevent cerebral palsy? N Engl J Med 2003;349:1765-69.
28. Clark SL, Hankin GDV. Temporal and demographic trends in cerebral palsy-fact and fiction. Am J Obstet and Gynecol 2003;72:865-68.
29. Thomas A, Saint-Anne-Dargassies S. Etudes neurologiques sur le nouveau-né et le jeune nourrisson. Paris: Montreal and Masson 1952:399-425.
30. Saint-Anne Dargassies S. Neurological development in the full-term and premature neonate. Amsterdam: Elsevier 1977: 74-93.
31. Prechtl HFR. Continuity and change in early neural development. U: Prechtl HFR. Continuity of neural functions from prenatal to postnatal life. London: MacKeith Press 1984:145-73.
32. Hadders-Algra M. General movement during prenatal and early postnatal life. U Kurjak A, Azumendi G (Eds). The fetus in three dimensions: Imaging, embryology, and fetoscopy. UK: Informa Health Care 2007:153-82.
33. Amiel-Tison C, Gosselin J. The Amiel-Tison and Gosselin neurological assessment and its correlations with disorders of higher cerebral function. U: Accardo PJ (Ed): Developmental disabilities in infancy and childhood. 3.izd. Baltimore: Paul H Brookes, 2007:124-41.
34. Gosselin J, Amiel-Tison C. Évaluation neurologique de la naissance à 6 ans. 2. izd. . Paris: Presses du CHUME Ste-Justine, Montréal and Masson 2007:46-61.
35. Amiel-Tison C, Gosselin J. Infante-Rivard C 2002: Head growth and cranial assessment at neurological examination in infancy. Dev Med Child Neurol 2002;44:64-81.
36. Gosselin J, Gahagan S, Amiel-Tison C. The Amiel-Tison neurological assessment at term: Conceptual and methodological continuity in the course of follow-up. Ment Retard Dev Disabil Res Rev 2005;11:34-54.
37. Amiel-Tison C. Correlation between hypoxic-ischemic events during fetal life and outcome. U: Arbeille P, Maulik D, Laurini R (Eds): Fetal Hypoxia. UK: Parthenon, Lancs 1999:246-73.
38. Einspieler C, Prechtl HFR, Bos AF, Ferrari F, Cioni G. Prechtl's method on the qualitative assessment of general movements in preterm, term and young infants. Cambridge: Mac Keith Press 2004:135-64.
39. Stahlmann N, Härtel C, Knopp A, Gehring B, Kiecksee H, Thyen U. Predictive value of neurodevelopmental assessment versus evaluation of general movements for motor outcome in preterm infants with birth weights <1500 gm. Neuropediatrics 2007;38:91-99.
40. Visser GH, Mulder EJ, Tessa Ververs FF. Fetal behavioral teratology. J Matern Fetal Neonatal Med 2010;23(Suppl 3): 14-16.
41. Visser GHA, Mulder EJH. Fetal movement patterns and fetal behavioural states. In: Wladimiroff JW, Eik-Nes S (Eds). Ultrasound in obstetrics and gynaecology. Elsevier, Philadelphia 2009;271-84.
42. Prechtl HFR. Qualitative changes of spontaneous movements in fetus and preterm infant are a marker of neurological dysfunction. Early Hum Dev 1990;23:151-58.
43. Hata T, Dai SY, Marumo G. Ultrasound for evaluation of fetal neurobehavioral development: From 2D to 4D ultrasound. Infant Child Dev 2010;19(1):99-118.
44. Prechtl HFR, Einspieler C. Is neurological assessment of the fetus possible? Eur J Obstet Gynecol Reprod Biol 1997;75: 81-84.
45. Andonotopo W, Kurjak A. The assessment of fetal behavior of growth restricted fetuses by 4D sonography. J Perinat Med 2006;34:471-78.
46. Kurjak A, Mišković B, Andonotopo W, Stanojević M, Azumendi G, Vrcić H. How useful is 3D and 4D ultrasound in perinatal medicine? J Perinat Med 2007;35:10-27.
47. Hata T, Dai SY, Marumo G. Ultrasound for evaluation of fetal neurobehavioural development: From 2D to 4D Ultrasound. Inf Child Dev 2010;19:99-118.
48. Kurjak A, Predojević M, Stanojević M, Salihagić Kadić A, Mišković B, Ahmed B, Talić A, Zaputović S, Honemeyer U. Intrauterine growth restriction and cerebral palsy. Acta Medica Informatica 2010;18:64-83.
49. Hata T, Kanenishi K, Tanaka H, Marumo G, Sasaki M. Four-dimensional evaluation of fetal neurobehavioral development. Donald School Journal of Ultrasound in Obstetrics and Gynecology 2010 (Accepted for publication).
50. Kurjak A, Vecek N, Hafner T, Boţek T, Funduk-Kurajak B, Ujević B. Prenatal diagnosis: What does four-dimensional ultrasound add? J Perinat Med 2002;30:57-62.
51. Kurjak A, Carrera J, Medic M, Azumendi G, Andonotopo W, Stanojević M. The antenatal development of fetal behavioral patterns assessed by four-dimensional sonography. J Matern Fetal Neonatal Med 2005;17:401-16.

52. Kurjak A, Pooh RK, Merce LT, Carrera JM, Salihagić-Kadić A, Andonotopo W. Structural and functional development assessed by three-dimensional and four-dimensional sonography. Fertil Steril 2005;84:1285-99.
53. Pooh RK, Kurjak A. Fetal neurology. New Delhi, Jaypee Brothers Medical Publishers 2009.
54. Hata T, Kurjak A, Kozuma S. Current topics on fetal 3D/4D ultrasound. Bentham Science Publishers Ltd 2009.
55. Kurjak A, Miskovic B, Stanojevic M, et al. New scoring system for fetal neurobehavior assessed by three- and four-dimensional sonography. J Perinat Med 2008;36:73-81.
56. Amiel-Tison C, Gosselin J, Kurjak A. Neurosonography in the second half of fetal life: A neonatologist's point of view. J Perinat Med 2006;34:437-46.
57. Kurjak A, Abo-Yaqoub S, Stanojevic M, Yigiter AB, Vasilj O, Lebit D, Shaddad AN, Ahmed B, Kavak ZN, Miskovic B, et al. The potential of 4D sonography in the assessment of fetal neurobehavior—multicentric study in high-risk pregnancies. J Perinat Med 2010;38:77-82.
58. Mišković B, Vasilj O, Stanojević M, Ivanković D, Kerner M, Tikvica A. The comparison of fetal behavior in high-risk and normal pregnancies assessed by four-dimensional ultrasound. J Matern Fetal Neonatal Med 2010 [Epub ahead of print].
59. Talić A, Kurjak A, Ahmed B, Stanojević M, Predojević M, Salihagić-Kadić A, DI Renzo GC. The potential of 4D sonography in the assessment of fetal behavior in high-risk pregnancies. J Matern Fetal Neonatal Med 2010 (Accepted for publication).
60. Kurjak A, Ahmed B, Abo-Yaguab S, Younis M, Saleh H, Shaddad AN, Vasilj O, Al Bahar AJ, Mišković B. An attempt to introduce neurological test for fetus-based on 3D and 4D sonography. Donald School Journal of Ultrasound in Obstetrics and Gynecology 2008;2:29-44.
61. Kurjak A, Tikvica Luetic A, Stanojević M, Talić A, Zalud I, Al-Noobi M, Perva S, Abushama M, Tomasovic S, Zaputovic S, Honemeyer U. Further experience in the clinical assessment of fetal neurobehavior. Donald School Journal of Ultrasound in Obstetrics and Gynecology 2010;4:59-71.