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REVIEW ARTICLE

Functional Test for Fetal Brain: The Role of KANET Test

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ABSTRACT

Defining normal and abnormal fetal neurological function *in utero* in order to better predict antenatally which fetuses are at risk for adverse neurological outcome has remained a great challenge in perinatal medicine. Fetal behavioral patterns have been considered as indicators of fetal brain development. It has been suggested that the assessment of fetal behavior in different periods of gestation may make possible the distinction between normal and abnormal brain development. Advances in ultrasound technology and particularly the introduction of real time four-dimensional (4D) ultrasonography, allowed direct observation of *in utero* life and offered a new insight for the assessment of fetal behavior. Fetal behavioral movements, the full range of facial expressions and mobility of fetal upper and lower extremities and fingers can be clearly visualized with 4D ultrasound. A new scoring system for the assessment of fetal neurobehavior based on prenatal assessment of the fetus with 4D sonography has been developed based on the same technique that neonatologists assess newborns during the first days of their postnatal life. This overview focuses on the study of fetal behavior and neurological assessment with 4D ultrasound.

Keywords: Fetal neurology, Neurobehavior, Four-dimensional ultrasound, KANET.

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INTRODUCTION

Fetal behavior is assessed through direct observation of movements and activities of the fetus *in utero*, with the use of ultrasound machines.[1-3] Advances of technology and especially of three-dimensional (3D) and four-dimensional (4D) ultrasound, have given the opportunity to study in real time and with explicit detail fetal anatomy and fetal activity. Studies have shown that there is a specific fetal behavioral pattern that corresponds to each week or trimester of *in utero* life and that this behavioral pattern reflects the process of human brain development and maturation.[4] The anatomic and functional development of the human brain is a uniquely complex and long lasting procedure that goes through very strict developmental stages, which starts from the second month of gestational age and continues up to adult life.[4] Development of the human brain is still incomplete at the end of *in utero* life and continues for decades after birth. The most important steps of human brain development are shown in Table 1. Human brain development is a very structured and detailed procedure, but as such it is at the same time very sensitive and susceptible to a wide variety of factors and defects, that may occur during any of the phases of intrauterine life. In cases of extremely premature neonates the brain development *ex utero* is unable to follow the genetically programmed growth pattern that the brain should have *in utero*, even when the postnatal environment and feeding mimics the conditions of *in utero* life.[5,6] Genetic factors, external stimuli, pathological conditions or even environmental changes, can affect the fetal human brain up to a degree that may be difficult to assess, especially prenatally. In many cases we are unable to detect fetal brain impairment, and even when we suspect it, again we are often unable to say in what way and to what extent will the fetus be affected. Brain injuries can occur prenatally, perinatally and/or even postnatally or neonatally. The neurological compromises that may result from such insults, may present with a wide variety of clinical pictures, ranging from mild behavioral and learning disabilities to severe cerebral palsy (CP).[4] Indeed, neurological disability is one of the most feared complications in perinatal medicine and its diagnosis antenatally is one of the greatest challenges in obstetrics. What is more, the cause and effect relationship of neurological disabilities, is often uncertain. The assessment of the integrity of the fetal nervous system is a major task in modern perinatal medicine.[6,7] Assessment of fetal behavior is time consuming, but only when normal behavior is well understood and documented, will be possible to compare it with abnormal cases, detect the differences between them, and as a result identify and perceive abnormal behavior before birth.

ULTRASOUND FOR THE ASSESSMENT OF FETAL BEHAVIOR

It has been well established that fetal behavioral patterns are directly related to the degree of development and maturation of the fetal nervous system,[8,9] while studies have shown, that the quality and quantity of fetal movements are very good indicators of neurobehavioral organization and as a result of the future neurological integrity of the fetus.[10-17] Two-dimensional (2D) ultrasound allowed the assessment of fetal anatomy and direct monitoring of fetal activity. Precht et al about 30 years ago were the first to study specific fetal movements with 2D ultrasound, performing the first steps in the area of fetal neurosonography, and preparing at the same time the ground for the study of fetal behavior *in utero*.[18] De Vries et al analyzed the qualitative and

Table 1: Major events in neural development

Developmental event	*Peak time of occurrence*
• Primary neurulation *(dorsal induction)*	3-4 weeks antenatally
• Prosencephalic cleavage *(ventral induction)*	5-6 weeks antenatally
• Neuronal proliferation	
Cerebral	2-4 months antenatally
Cerebellar	2-10 months postnatally
• Neuronal migration	
Cerebral	3-5 months antenatally
Cerebellar	4-10 months antenatally
• Neuronal differentiation	
Axon outgrowth	3 months—birth
Dendritic growth and synapse formation	6 months—1 year postnatally
• Synaptic rearrangement	Birth—years postnatally
• Myelination	Birth—years postnatally

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quantitative aspects of fetal movements and reported not only how to describe a particular movement, but also how these movements were performed in terms of speed and amplitude and participating body movements.[19-21] It has been suggested that assessment of fetal behavior during different periods of gestation could make it possible to distinguish between normal and abnormal brain development.[21-24]

Since then technology has made huge progress and has offered many options for fetal surveillance, while the development of new ultrasound techniques has allowed direct visualization of the fetus *in utero*.[25-27] However, 2D ultrasound with poor quality images was considered to be somewhat subjective, because the information needed observer's interpretation.[24] The overcoming of these problems was made possible with the introduction of 3D/4D ultrasound technology, which has been imported in everyday practice and is an important part of routine ultrasound assessment of the fetus. In contrast to 2D ultrasound, 3D visualization of the fetus provides better pictures and real time images that help not only to visualize the fetal anatomy in a much better way than 2D ultrasound, but also to evaluate the movements and the behavior of the fetus *in utero*.[28] Studies have shown that 4D ultrasound offers a practical mean of assessment of both brain anatomy and function, with more details and at a much earlier gestational age than 2D ultrasound does.[29] It has been proven that 4D sonography can assist in the better understanding of both the somatic and motor development of the fetus and has led to very important conclusions concerning fetal behavior by enabling us to produce measurable parameters for the assessment of normal neurobehavioral development.[30] What is more, 4D ultrasound, by obtaining real time images, allows spatial observations of fetal face (e.g. smiling, crying, mouthing and blinking), something that cannot be achieved with 2D ultrasound, and multicenter studies have verified that with the use of 4D ultrasound it is feasible to distinguish between normal and abnormal behavioral patterns of the fetus, which could eventually lead to early diagnosis of brain impairment.[31,32] The advantages of 3D and 4D ultrasound for the assessment of fetal anatomy and fetal behavior, has been shown by large studies.[55]

It is known that fetal movements occur much earlier than the time that mothers can feel them, even during the embryonic period.[26] The pattern, the quantity and the quality of fetal movements are growing rapidly throughout pregnancy, starting with gross, asynchronized movements of the whole embryo and leading to organized and detailed movements, as well as facial expressions toward the end of the pregnancy.[33] Studies regarding neonatal neurology have shown that the assessment of neonatal behavior is a better predictor of neurodevelopmental disability than neurological examination. These findings initiated a series of studies that aimed to find the relationship of fetal behavior and developmental processes during specific periods of gestational age, in order to make possible the distinction between normal and abnormal brain development, and also to enable early diagnosis of various structural or functional abnormalities of the fetal nervous system.[1-4,18-23,57] About 5 years ago the Zagreb group developed a structured and systematic way for assessing the integrity of the fetal central nervous system, by using 4D ultrasound.[34] This new test was called Kurjak's antenatal neurodevelopment test (KANET), and its innovation is that it assesses the fetus *in utero* in the same way that neonates are examined postnatally for brain damage, incorporating parameters from neonatal neurological tests (Amiel-Tison), with the use of 4D ultrasound.[35-37]

KURJAK ANTENATAL NEURODEVELOPMENTAL TEST (KANET)

Timely diagnosis of brain impairment is the main reason why so many studies have been conducted regarding the

anatomical and functional integrity of the fetal nervous system and the understanding of fetal behavior. Based on the results of these studies, scientists have eventually been led to the development of methods for the assessment of fetal and neonatal behavior.[1] KANET is a new scoring system for the assessment of fetal neurobehavior that was developed by the Zagreb group. This test has been recently introduced and is based on prenatal evaluation of the fetus by 3D/4D ultrasound.[34] This scoring system is a combination of some parameters consisting of fetal general movements (GMs) and of postnatal Amiel-Tison Neurological Assessment at Term (ATNAT) signs, which can be easily visualized prenatally by using 4D ultrasound.[35,39] The following parameters have been incorporated in the KANET test: isolated head anteflexion, overlapping cranial sutures, head circumference, isolated eye blinking, facial alterations, mouth opening (yawning or mouthing), isolated hand and leg movements and thumb position, Gestalt perception of GMs (overall perception of the body and limb movements with their qualitative assessment).

Several papers have shown that there is a continuity of behavior from pre- to postnatal life and it has been observed that all movements that are present at neonates are also present in fetal life, with the exception of Moro's reflex, which cannot be demonstrated in fetuses.[40] This is probably due to a different environment to which fetus and neonate are exposed. The fetus lives in an environment of microgravity, while the newborn is exposed to full gravity, which creates certain obstacles for neurodevelopment in the first months of life.[6] The parameters were chosen based on developmental approach to the neurological assessment and on the theory of central pattern generators of GMs emergence, and were the product of multicentric studies conducted for several years.[38,39] KANET is a combination of assessments of fetal behavior, GMs and three out of four signs which have been postnatally considered as symptoms of possible neurodevelopmental impairment (neurological thumb, overlapping sutures and small head circumference).[41]

KANET test was standardized in Osaka, Japan on the 24th of October 2010, in order for the test to become reproducible and easily applied by fetal medicine specialists.[41] According to the Osaka Consensus Statement the KANET should be performed in the 3rd trimester of pregnancy, between 28 and 38 weeks. The duration of the examination should be between 15 and 20 minutes, and fetuses should be examined while they are awake. If the fetus is in the sleeping period, the assessment should be postponed for 30 minutes or for the following day, at a minimum period of 14 to 16 hours. In cases of grossly

Fig. 1: Normal KANET score at 34 weeks of pregnancy

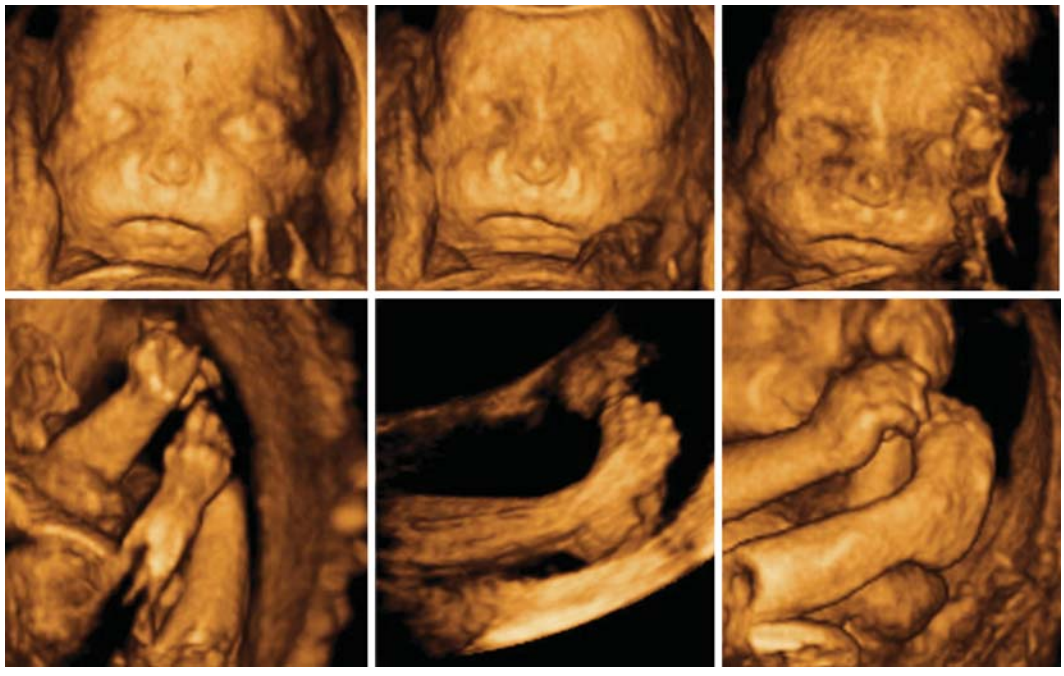
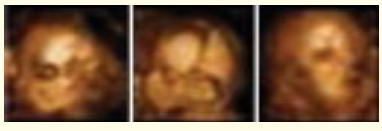


Fig. 2A: Abnormal KANET score at 28 weeks of a fetus with severe hydranencephaly after CMV infection. No facial alterations or mouth movements were identified ('frozen face or face like mask'), fists remained clenched and no leg movements were seen (right foot deviated inward–club foot)

Fig. 2B: Abnormal KANET score at 31 weeks of gestation, of a fetus with semilobar holoprosencephaly. Mouth movements were identified (tongue expulsion), but otherwise facial alterations were minimal and the KANET score was abnormal (KANET score = 4). No leg movements were seen and neurological thumb was identified. Neonate died 3 days after delivery

abnormal or of borderline score, the test should be repeated every 2 weeks until delivery. Special attention should be paid to the facial movements and to eye blinking, which are prenatally very informative and important ('the face is the mirror of the brain'). The frequency of facial and mouth movements should be 0 to 5 and more than 5. Overall number of movements should be defined in very active or inactive fetuses and compared with normal values of previous studies.[38,39] (Figs 1 and 2). All the examiners should have extensive hands-on education for the application of KANET test, both in low and in high-risk pregnancies. Interobserver and intraobserver variability

Table 2: Proposal for the new KANET assessment tool consisting of eight parameters

Sign	*Score*			*Sign score*
	0	*1*	*2*	
Isolated head anteflexion 	Abrupt	Small range (0-3 times of movements)	Variable in full range, many alteration (>3 times of movements)	
Cranial sutures and head circumference 	Overlapping of cranial sutures	Normal cranial sutures with measurement of HC below the normal limit (–2 SD) according to GA	Normal cranial sutures with normal measurement of HC according to GA	
Isolated eye blinking 	Not present	Not fluent (1-5 times of blinking)	Fluency (>5 times of blinking)	
Facial alteration (grimace or tongue expulsion)  or mouth opening (yawning or mouthing) 	Not present	Not fluent (1-5 times of alteration)	Fluency (>5 times of alteration)	
Isolated leg movement 	Cramped	Poor repertoire or small in range (0-5 times of movement)	Variable in full range, many alternation (>5 times of movement)	
Isolated hand movement 				

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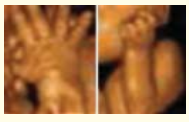
Sign	Score			Sign score
	0	1	2	
or hand to face movements 	Cramped or abrupt	Poor repertoire or small in range (0-5 times of movement)	Variable in full range, many alternation (>5 times of movements)	
Fingers movements 	Unilateral or bilateral clenched fist, (neurological thumb)	Cramped invariable finger movements	Smooth and complex, variable finger movements	
Gestalt perception of GMs	Definitely abnormal	Borderline	Normal	
			Total score	

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should be available. It is advisable to use 4D ultrasound machines, with frame rate of minimum 24 volumes/second. The Osaka Consensus Statement concluded that the KANET should use eight parameters rather than 10, for the assessment of the fetus (Table 2). A score range of 0 to 5 is characterized as abnormal, a score calculated from 6 to 13 is considered borderline and a score range of 14 to 20 is normal (Table 3). After that neonates should be followed up postnatally for neurological development for a 2 years period.

The test evaluates quantitative as well as qualitative aspects of fetal motor behavioral patterns. This technique supplies more convincing images/video sequences than conventional ultrasonic and nonultrasonic methods, enabling to observe fetal movements in their full repertoire and variability. The parameters examined by this test are partly based on observation of GMs. A second group of parameters is adopted from ATNAT.[42,43] The criterion of quality and quantity of spontaneous GMs is believed to have excellent reliability in evaluating the integrity of fetal CNS.[22,44] Furthermore, a continuity of behavioral patterns from prenatal to the postnatal period has been proven.[45-47] This continuity allows the ultrasonography to derive a fetal assessment from newborn neurologic findings. Both those facts justify the choice of the parameters used in this test, making KANET theoretically appropriate for the assessment of fetal behavior. According to previous reports[48-53] KANET easily recognizes serious functional impairment associated with structural abnormalities. Recent studies have shown that the application of KANET in both low and high risk populations has given very promising results about the

Table 3: Interpretation of KANET scores

Total score	Interpretation
0-5	Abnormal
6-9	Borderline
10-16	Normal

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outcome of the fetuses and especially in high risk populations, the result of KANET may provide extremely useful information and guidelines for the counseling of the neurological outcome of these fetuses.[54] The KANET is the first test which is based on 4D ultrasound, with an original scoring system and has been standardized, so it can be implemented in everyday practice, overcoming the practical difficulties and covering the gaps of methods that were used in the past for the evaluation of fetal behavior.[56-59] More recent studies show evidence that KANET is easily applicable to the majority of pregnancies, the learning curve is short for physicians who already have training in obstetrical ultrasound and the actual time of the KANET is very reasonable, ranging from 15 to 20 minutes, showing strong evidence that it can be widely implemented for fetal neurological assessment.[52] As a conclusion, the results of recent, large multicenter studies show that KANET is an easily applied, standardized test, which utilizes the advantages of 4D ultrasound, such as better analysis of facial expressions and quality (variability and complexity) of fetal movements, in order to distinguish between normal and abnormal behavioral patterns of the fetus, with the aim of early recognition of fetal brain impairment.[41]

EVIDENCES OF PRENATAL DETECTION BY MULTICENTRIC STUDIES

One of the first studies to use a preliminary form of the KANET scoring system was that by Andonotopo et al in 2006. They aimed to assess fetal facial expression and quality of body movements and examine if they are of diagnostic value for brain impairment in fetuses with growth restriction. In that prospective study of 50 pregnancies with intrauterine growth restriction (IUGR) fetuses in the 3rd trimester of pregnancy, a tendency of less behavioral activity in IUGR than normal fetuses has been noted. The results of the study encouraged future investigation of the use of 4D ultrasound for quantitative and qualitative assessment of fetal behavior as possible indicators of the neurological condition in IUGR fetuses.[53]

The Zagreb group in 2008, were the first to introduce the KANET for the assessment of neurological status of the fetus, aiming to the detection of fetal brain and neurodevelopmental alterations due to *in utero* brain impairment. In order to develop the new scoring system they identified severely brain damaged neonates and neonates with good neurological condition and then compared the neonatal findings, with corresponding findings *in utero*. In the group of 100 low-risk pregnancies they retrospectively applied KANET. After delivery, postnatal neurological assessment (ATNAT) was performed and all neonates assessed as normal reached a score between 14 and 20, which was assumed to be the score of optimal neurological development. New scoring system was applied in the group of 120 high-risk pregnancies in which, based on postnatal neurological findings, three subgroups of newborns were identified: normal, mildly or moderately abnormal and abnormal. Based on this, a neurological scoring system has been proposed. All normal fetuses reached a score from 14 to 20. Ten fetuses who were postnatally described as mildly or moderately abnormal achieved a prenatal score of 5 to 13, while another 10 fetuses postnatally assigned as neurologically abnormal had a prenatal score 0 to 5. Among this group four had alobar holoprosencephaly, one had severe hypertensive hydrocephaly, one had thanatophoric dysplasia and four fetuses had multiple malformations. This study inspired a large series of multicenter studies (Table 4) that used the KANET in order to assess the usefulness of this promising new scoring system for the assessment of neurological status in fetuses and the recognition of signs of early brain impairment *in utero*.[25,32]

The results of the first multicenter study, which included 288 high-risk pregnancies, from four different centers, were published in 2010. They identified seven cases with abnormal KANET and 25 cases with borderline KANET score, yielding 32 fetuses at neurological risk. There were also 11 cases with abnormal KANET, of which six fetuses died *in utero* and five were terminated. The seven remaining neonates with abnormal KANET were followed up postnatally at 10 weeks and out of these seven cases, three were found to have abnormal ATNAT scoring postnatally. These were a case of arthrogryposis, a case of vermis aplasia and a fetus whose previous sibling had verified CP. The fetuses in these three cases had especially reduced facial movements–the faces were like masks during the ultrasounds. The remaining four cases were considered normal (ventriculomegaly, pre-eclampsia, thrombophilia, oligohydramnios). Out of 25 borderline KANET there were 22 borderline newborns by ATNAT, whereas three were normal (ventriculomegaly, syndrome of intra-amniotic infection, maternal thrombocytopenia). Those who were abnormal prenatally and normal postnatally had the following prenatal risk-factors: ventriculomegaly, Dandy-Walker malformation, skeletal dysplasia, polyhydramnios, gestational diabetes, hydrocephaly, thrombophilia, pre-eclampsia, achondroplasia, oligohydramnios, nonimmune hydrops, intra-amniotic infection, IUGR, trisomy 21, thrombocytopenia. Out of three abnormal neonates after ATNAT assessment two had definitely abnormal Prechtl's premature GMs (arthrogryposis and vermis aplasia) and an additional six were considered abnormal (neonate of the mother with the previous child with CP, Dandy-Walker syndrome, hydrocephaly, trisomy 21, ventriculomegaly, nonimmune hydrops). The remaining 21 children had normal optimal or normal suboptimal GMs. During their study they also followed the pregnancy of a fetus with acrania, which the mother had refused to terminate due to religious reasons, documenting the evolution of the fetal behavior from 20 weeks and as the motor control was shifting from the lower to the upper control center the fetus ended up with a very low KANET score. The authors reached the conclusion that there is a potential for antenatal detection of serious neurological conditions, especially in identifying the fetuses from high-risk pregnancies at neurological risk.[48]

Miskovic et al applied KANET in 226 cases, both high- and low-risk pregnancies and compared the results. They found three cases of abnormal KANET, that had chromosomal abnormalities and all three had abnormal ATNAT, as well. The KANET scores from both groups were compared to the results of the ATNAT tests, and found statistically significant difference among the low and the high risk groups, for eight out of the 10 KANET parameters (isolated anteflexion of the head, eye blinking, facial expressions–grimacing, tongue expulsion, mouth movement

Table 4: List of studies that have applied KANET test to different populations

Author	*Year*	*Study*	*Study design*	*Study population*	*Indication*	*No*	*GA (weeks)*	*Time (mins)*	*Result*	*Summary*
Kurjak et al[15]	2008	Cohort	Retrospective	High-risk	Multiple	220	20-36	30	Positive	A new scoring system was proposed for the antenatal assessment of fetal neurological status
Kurjak et al[28]	2010	Multicenter	Prospective	High-risk	Multiple	288	20-38	30	Positive	KANET appeared to be prognostic of antenatal detection of serious neurological fetal problems. KANET also identified fetuses with severe structural abnormalities, especially associated with brain impairment
Miskovic et al[32]	2010	Cohort	Prospective	High-risk	Multiple	226	20-36	30	Positive	Correlation between antenatal (KANET) and postnatal (ATNAT) results was found. KANET showed differences of fetal behavior between high- and low-risk pregnancies
Talic et al[31]	2011	Multicenter Cohort	Prospective	High-risk	Multiple	620	26-38	15-20	Positive	KANET test had a prognostic value in discriminating normal from borderline and abnormal fetal behavior, in normal and in high risk cases. Abnormal KANET scores were predictable of both intrauterine and postnatal death
Talic et al[29]	2011	Multicenter Cohort	Prospective	High-risk	Ventriculo-megali	240	32-36	10-15	Positive	Statistically significant difference was identified in KANET scores between normal pregnancies and pregnancies with ventriculomegaly. Abnormal KANET scores and most of the borderline scores were noted in fetuses with severe ventriculomegaly, especially associated with additional abnormalities
Honemeyer et al[39]	2011	Cohort	Prospective	Unselected	Unselected	100	28-38	N/A	Positive	Normal prenatal KANET scores had a significant predictive value of a normal postnatal neurological evaluation
Lebit et al[14]	2011	Cohort	Prospective	Low-risk	Normal 2D examination	144	7-38	15-20	Positive	A specific pattern of fetal neurobehavior corresponding to each trimester of pregnancy was identified

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Author	*Year*	*Study*	*Study design*	*Study population*	*Indication*	*No*	*GA (weeks)*	*Time (mins)*	*Result*	*Summary*
Abo-Yaqoub et al[50]	2012	Cohort	Prospective	High-risk	Multiple	80	20-38	15-20	Positive	Significant difference in KANET scores was noted. All antenatally abnormal KANET scores had also an abnormal postnatal neurological assessment
Vladareanu et al[61]	2012	Cohort	Prospective	High-risk	Multiple	196	24-38	N/A	Positive	Most fetuses with normal KANET→low-risk, those with borderline→IUGR fetuses with increased MCA RI and most fetuses with abnormal KANET→threatened PTD with PPROM. Difference in fetal movements was identified between the two groups. For normal pregnancies→ 93.4% of fetuses achieved normal score, for high-risk pregnancies→78.5% of fetuses had a normal score
Honemeyer et al[62]	2012	Cohort	Prospective	High- and low-risk	Multiple	56	28-38	30 max	Positive	Introduction of the average KANET score→combination of the mean value of KANET scores throughout pregnancy Revealed a relationship of fetal diurnal rhythm with the pregnancy risk
Kurjak et al[73]	2013	Cohort	Prospective	High- and low-risk	Multiple	869	28-38	20	Positive	Statistically significant differences in the distribution of normal, abnormal, and borderline KANET scores between low-risk and high-risk groups were found. Fetal behavior was significantly different between the normal group and the high-risk subgroups
Predojevic et al[75]	2013	Case study	Prospective	High-risk	IUGR	5	31-39	30	Positive	KANET could recognize pathologic and borderline behavior in IUGR fetuses with or without blood flow redistribution. Combined assessment of hemodynamic and motoric parameters could enable in better diagnosis and consultation

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Author	Year	Study	Study design	Study population	Indication	No	GA (weeks)	Time (mins)	Result	Summary
Athanasiadis et al[74]	2013	Cohort	Prospective	Unselected (High- and low-risk)	Multiple (IUGR, PET, GDM)	152	2nd and 3rd trimester	N/A	Positive	The neurodevelopmental score was statistically significant higher in the low-risk group compared to the high-risk group ($p < 0.0004$). The diabetes subgroup score was statistically significantly higher compared to the IUGR and the pre-eclampsia subgroup ($p = 0.0001$).

KANET: Kurjak's antenatal neurological test; No: number of patients; IUGR: intrauterine growth restriction; MCA: middle cerebral artery; PTD: preterm delivery; PPROM: preterm premature rupture of membranes; PET: pre-eclampsia; GDM: gestational diabetes mellitus

such as yawning, jawing, swallowing–isolated hand movements, hand to face movements, fist and finger movements and GMs). Comparison of KANET and ATNAT showed statistically significant, moderate correlation between the two tests, which means that the neuropediatric exam (ATNAT) confirmed the prenatal findings of 4D ultrasound examination (KANET). The authors concluded that these preliminary results were promising and stated that further studies are needed before the test could be recommended for wider clinical practice.[52]

Talic et al around the same period, in a multicenter study, published the largest series of KANET so far, with 620 singleton pregnancies, both low and high risk cases (100 low risk and 520 high risk cases), excluding however fetuses with structural abnormalities, that were studied between 26 and 38 weeks of gestation. Fetuses with congenital anomalies multiple pregnancies were excluded from the study. The high risk group of patients consisted of the following subgroups: threatened preterm delivery with or without preterm rupture of membranes (PPROM), previous child diagnosed with CP, hypertension in pregnancy with or without pre-eclampsia, diabetes before pregnancy or gestational diabetes, intrauterine growth restriction, polyhydramnios, Rhesus isoimmunization, placental bleeding and maternal fever >39°C. Analysis of the data confirmed statistically significant difference in the distribution of fetal KANET scores between the two populations. Impressively the largest incidence of fetuses with abnormal KANET was noticed in the subgroup of participants with a previous child diagnosed with CP (23.8%) and the largest incidence of fetuses with borderline KANET was observed in the subgroup of mothers with fever (56.4%). The following parameters of KANET test significantly differed between the fetuses from low- and high-risk pregnancies: overlapping cranial sutures, head circumference, isolated eye blinking, facial expressions, mouth movements, isolated hand movements, isolated leg movements, hand to face movements, finger movements and GMs. The authors observed that a low KANET score is predictive of both intrauterine or neonatal death–they had two intrauterine deaths in fetuses with low KANET (scores of 3 and 4 respectively) and one neonatal death (with a KANET score of 2). In 10 out of 36 fetuses with abnormal KANET after 2 and 6 months, postnatal neurological examination indicated severely abnormal finding: four of them had severe generalized spasticity. The study demonstrated the potential of KANET to detect and discriminate normal from borderline and abnormal fetal behavior in normal and in high-risk pregnancies. Other neonates are still followed up in this study, in order to reach safe conclusions.[51]

Honemeyer et al studied 100 fetuses, who underwent, between 28 and 38 weeks of gestation, up to three times during their pregnancy assessment by KANET. The fetuses were followed-up postnatally, immediately after delivery and again at 12 weeks of life, with systematic neurological assessment by the neonatologist. The results from the scoring systems of pre- and postnatal evaluation were compared. Results showed that a normal prenatal KANET score is significantly predictive of normal postnatal neurological assessment of the newborn immediately after delivery and at 12 weeks of life. The authors concluded that that normal antenatal KANET scores is a very good predictor of a normal postnatal neurological outcome.[60]

Lebit et al used part of the KANET to assess fetal movements throughout pregnancy in 144 low-risk pregnancies, between 7 and 38 weeks of gestation, concluding to a specific pattern of fetal behavior for each trimester of pregnancy.[33] The authors noticed that in the first trimester fetal movements grow rapidly in frequency

and complexity, while in the second half of pregnancy the motor behavior significantly increases in frequency and variability. Facial expressions and eye movements also appear in second trimester, with the first eye movements starting at about 18 weeks. In late pregnancy fetal movements show a decline and the periods of rest start to grow. This decrease is rather a consequence of the brain maturation process rather than reduced amount of amniotic fluid.[25,26] They concluded that dynamic evaluation of fetal behavior reflects directly the processes of maturation and development of the central nervous system and that KANET test has much to offer in the assessment of fetal behavior.[33]

A very important study was that by Talic et al which aimed to assess the differences in fetal behavior in both normal fetuses and fetuses with cerebral ventriculomegaly, by using KANET. They studied 240 fetuses between 32 and 36 weeks of gestation, 140 fetuses with ventriculomegaly and 100 normal fetuses. Six percent of the fetuses from the low risk-control group had pathological KANET scores, while 34.9% of the fetuses with ventriculomegaly had pathological KANET. The largest number of abnormal KANET scores was found in 22 fetuses with severe ventriculomegaly, accompanied by other structural abnormalities (Dandy-Walker, Arnold-Chiari, agenesis of the corpus callosum, holoprosencephaly, encephalocele, spina bifida, choroid plexus cyst, osteogenesis imperfect type II, thanatophoric dysplasia type I and Meckel-Gruber syndrome). There were no fetuses with abnormal KANET in the group of isolated mild and moderate ventriculomegaly. The authors concluded that prenatal neurological findings of the fetuses by application of KANET test is in concordance with their postnatal outcome and that evaluation of fetal behavior by KANET in fetuses with cerebral ventriculomegaly had the potential to detect fetuses with abnormal behavior, adding a functional dimension of the central nervous system evaluation to the brain morphology. Also the degree of ventriculomegaly and the presence of coexisting congenital malformations, appeared to be important factors determining the final KANET score. The results of this study were very positive and showed that KANET could provide useful information for the correct assessment and counseling of patients with a common finding, such as ventriculomegaly, the significance of which is not well defined.[54]

More recently, Abo-Yaqoub et al studied 40 pregnant women with high-risk pregnancies for neurological abnormalities, between 20 and 38 weeks of gestation using KANET scoring system and compared the results with 40 low risk cases, in order to determine the role of 4D ultrasound in prenatal assessment of fetal neurobehavior and in the prediction of adverse neurological outcome. The difference in the range of KANET score was significant between the two groups and all cases with abnormal KANET proved to be abnormal postnatally, whereas those with normal or borderline KANET scores were neurologically normal at least in the early neonatal period that they were assessed. The parameters that were significantly different between the two groups were: isolated head anteflexion, isolated eye blinking, facial expressions, mouth movements, isolated hand movements hand-to-face movements, finger movements and GMs. For isolated leg movements and cranial sutures, the difference was not significant.[50]

Vladareanu et al applied KANET in 196 singleton pregnancies (61 low risk and 135 high-risk patients) between 24 and 38 weeks of gestation in a period of 3 years. Most fetuses in the study who obtained normal KANET score belonged to the low-risk pregnancies, those who obtained borderline score were fetuses with IUGR and with increased resistance index (RI) of middle cerebral artery (MCA) and most fetuses with abnormal KANET score derived from pregnancies complicated by threatened preterm delivery with PPROM. There was statistical significant difference in fetal movements in the two groups. In normal pregnancies, most fetuses (93.4%) achieved a normal KANET score compared to 78.5% of the fetuses from high-risk pregnancies. Borderline and abnormal scores were dominant in high-risk pregnancies. In the high-risk pregnancy group, most abnormal KANET scores were in pregnancies complicated by threatened preterm delivery with PPROM (25%). Most fetuses with pregnancies complicated by IUGR with MCA RI index changes and with hypertension above 160/100 mm Hg achieved borderline score (50%). The highest percentage of normal fetal movements was found in pregnancies complicated by Rh isoimmunization without hydrops fetalis (96%). The characteristics of reduced speed and amplitude were found in the threatened preterm delivery group. There was a reduction of both number and duration of GMs in the IUGR group. The IUGR fetuses moved less and their GMs were poorly organized. Alterations in the quality of fetal movements were accompanied by considerable decrease in the quantity of fetal movements. The authors concluded that KANET can be useful for early diagnosis of neurological disorders that become manifest in perinatal and postnatal period.[61]

Honemeyer et al studied 56 singleton pregnancies (24 low-risk and 32 high-risk cases) between 28 and 38 weeks of gestation and applied serial KANETs on them, performing a total of 117 tests in total. They did not identify any abnormal KANET scores, but two thirds of the borderline scores occurred in the high-risk pregnancies. Because they

performed more than one KANET in each pregnancy they introduced the average KANET score, which derived from the scores of each fetus during pregnancy. Only one fetus had a borderline average KANET score, and this fetus who belonged to the high-risk group, was the only one out of 56 pregnancies who had an abnormal early neurological outcome. When the authors compared all the 18 borderline KANET scores with fetal diurnal rhythm based on maternal observation, they noticed that 89% of the borderline scores of the at-risk group were recorded at times that the mothers characterized them as active periods, compared with 33.3% in the low-risk pregnancies. The authors concluded that KANET is suggestive of expressing the risk for neurodevelopmental fetal disorders, but the connection of fetal diurnal rhythm and pregnancy risk status should be investigated further.[62]

Kurjak et al studied 869 high- and low-risk singleton pregnancies taking under consideration the results of the Doppler studies of umbilical and middle cerebral arteries, and noticed that fetal behavior was significantly different between the normal group and the following subgroups of fetuses: fetal growth restriction (FGR), gestational diabetes mellitus, threatened preterm birth, antepartum hemorrhage, maternal fever, sibling with CP, and polyhydramnios.[73] The authors concluded that their study showed a new clinical application of the KANET test in early identification of fetuses at risk for adverse neurological outcome.

FIVE-YEAR VIEW

KANET appears to be a diagnostic tool of great potential for obstetricians, particularly for the detection of problems that were inaccessible any other method until now by, such as fetal brain impairment and neurodevelopmental alterations.[39] Of course as a new method, additional studies in large populations are needed before recommending the test in routine clinical practice. So far, studies have shown that KANET is useful for the standardization of neurobehavioral assessment, with the potential of detecting antenatally fetuses with severe neurological impairment,[26,46,49] and that introduction of KANET in clinical practice at least for the assessment of high-risk pregnancies is feasible. Ongoing studies aim to further investigate the potential of this new method setting the guidelines for a complete fetal neurosonography and neurobehavior assessment.[72] The continuous knowledge that we gain by studying fetal neurobehavior in a systematic way with the application of a standardized method such as KANET, in combination with the unrelenting technological advantage of 4D ultrasonography gives the impression that in the near future perinatal medicine will be able to give answers to the everlasting problem of assessing functional development of the fetal nervous system.

EXPERT COMMENTARY

One of the greatest challenges of obstetrical ultrasonography is the better understanding of fetal neurological function.[37,63] Neurological problems, such as CP are poorly understood and often falsely attributed to intrapartum events, while for the majority of CP cases it has been proven that the causative pathway starts long before delivery.[64-66] Several attempts have been made in order to define normal and abnormal fetal neurological function and to develop a method of assessment of the integrity of the fetal nervous system, but still without satisfactory sensitivity.[48,65-67]

Fetal behavioral patterns are directly reflecting developmental and maturational processes of fetal central nervous system.[65-67] What is more, studies have shown that there is continuity between fetal and neonatal neurobehavior. It has been suggested that the assessment of fetal behavior during different periods of gestation may provide valuable information about normal and abnormal brain development, and contribute to the early diagnosis of various structural or functional neurological abnormalities.[19] Technological advances in ultrasonography, particularly the introduction of high quality 3D and 4D ultrasound, allowed the study of fetal anatomy in explicit detail and the real time observation of the fetal behavior. The viewing of details of the fetal face, and especially movements of mouth, eyes (facial expressions) and fingers have been made possible with the introduction of 4D ultrasound.[68-71] KANET is the first method that attempted to use 4D ultrasound in order to assess and combine parameters of fetal behavior and form a scoring system that would assess the fetus in a comprehensive and systematic approach, in the same way that neonatologists perform a neurological assessment in newborns during the first days of their life, in order to determine their neurological status.[33] KANET appears to be able to identify functional characteristics of the fetus that predict normal and abnormal neurological development and hopefully future results of the prospective multicentric studies that are taking place at the moment in the next few years it will provide more information on fetal neurology. Such information will be of great value in counseling mothers of high risk pregnancies, like for example in cases with previous child with CP and also provide valuable evidence for cases of litigation.

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