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REVIEW ARTICLE

The Assessment of Fetal Neurobehavior with Four-dimensional Ultrasound: The Kurjak Antenatal Neurodevelopmental Test

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ABSTRACT

Fetal neurology is an evolving field in prenatal diagnosis and fetal medicine with great interest. The identification and diagnosis of brain damage prenatally has been a great challenge in obstetrics for many years and early identification of this damage would have implications on the perinatal management and is of great importance in cases of medical litigation. Defining normal and abnormal fetal neurological function *in utero* in order to better predict antenatally which fetuses are at risk for adverse neurological outcome still is under investigation. Several attempts have been made in the past to form a system that could detect fetuses with compromised central nervous system (CNS) function or brain impairement. Assessment of fetal behavior gave a promising opportunity to understand the hidden function of the developmental pathway of the fetal CNS. The assessment of normal neurobehavioral development by four-dimensional (4D) ultrasound gave the opportunity to investigate functional characteristics of the fetus that could predict neurological developmental dysfunction. These series of studies lead to the formation of Kurjak's antenatal neurodevelopmental test (KANET). KANET combines the assessment of fetal behavior, general movements and three out of four signs that have been postnatally considered as symptoms of possible neurodevelopmental impairment (neurological thumb, overlapping sutures and small head circumference). Assessment of fetal behavior by 4D ultrasound and application of KANET scoring test has been recently published in several journals and summarized results are presented in this review.

Keywords: Four-dimensional ultrasound, KANET, Fetal neurology, Cerebral palsy.

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INTRODUCTION

The study of fetal nervous system has been a great challenge for obstetricians and neonatologists for many years.[1-3] Human brain development is a very structured process that follows a certain series of events, starting from the induction of neuroectoderm to the formation of synapsis and wiring of the neurons.[4] The most important steps of human brain development and the peak times of their occurrence are shown in Table 1. The extreme complexity of human brain begins its evolution after the establishment of the essential external form. The events that follow mainly involve proliferation of the brain's total complement of neurons, migration of those neurons to specific sites throughout the central nervous system (CNS), organizational events that result in the intricate circuitry characteristics of human brain and finally the ensheathment of this circuitry, with the neural specific membrane called myelin. These events occur throughout a long period of time, starting from the second month of gestational age and extending to adult life.[4] Defects in brain development may arise during any of the phases of intrauterine life. It is well-established that the human brain is susceptible to a wide variety of genetic, developmental and acquired abnormalities and insults. The human brain is very sensitive to environmental changes that affect its growth and development. The brain of extremely premature neonates is unable to follow the genetically programmed growth pattern, even when postnatal feeding and nurturing of the neonates is conducted.[5,6] 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 the most feared complication of pregnancy, labor and neonatal period. The cause and effect relationship of neurological disabilities, however, is often uncertain. It has been clarified that some groups of fetuses/neonates are more

Table 1: Major events in neural development[4]

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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susceptible to neurological problems than others. Extremely preterm babies have a 100-fold increased risk of CP compared with term neonates, while the prevalence of CP is higher in term infants born at 37, 38, 39, 41 and 42 weeks compared with those born at 40 weeks.[6,7] Clinical and epidemiologic studies have shown that in almost 90% of CP cases, the causative pathway in contrast to what it was thought in the past is not related to intrapartum events. The assessment of the integrity of the fetal nervous system is a major task in modern perinatal medicine. There are many good reasons for that. One of them is that 2 to 4 out of 1000 newborns are affected by CP and this number has not decreased for many years. Despite earlier optimism that CP was likely to disappear with the advent of improvements in obstetrical and neonatal care, there has been no consistent decrease in frequency in the past several decades and surprisingly the incidence of CP cases has not changed since 1951.[4] Although the brain injury that initially causes CP by definition does not progressively worsen through the patient's lifetime, CP is a lifelong disability with diversified manifestations throughout lifespan. That is one among many justifiable reasons for prevention and earlier detection of CP.[6,7]

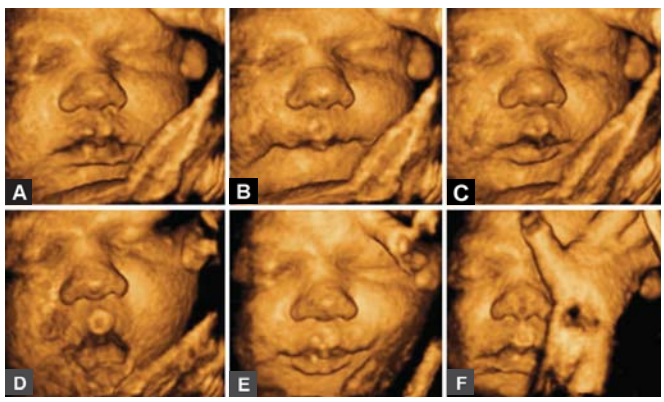
The Role of Ultrasound for the Assessment of Fetal Behavior

Several attempts have been made in the past to initiate a prenatal screening system that could detect fetuses with compromised CNS function and brain impairment. Studies have shown that fetal behavioral patterns directly reflect developmental and maturational processes of the fetal CNS.[8,9] More specifically, the development of fetal movement patterns has been described as a major maturational process and a sensitive indicator of neurobehavioral organization and future temperamental and cognitive status of the fetus.[10-17] The introduction of two-dimensional (2D) ultrasound in obstetrics allowed direct visualization of fetal anatomy and monitoring of fetal activity. Precht et al[18] 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*. De Vries et al[19-21] analyzed the qualitative and 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. 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 three-dimensional (3D)/four-dimensional (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 have been shown by large studies.[55]

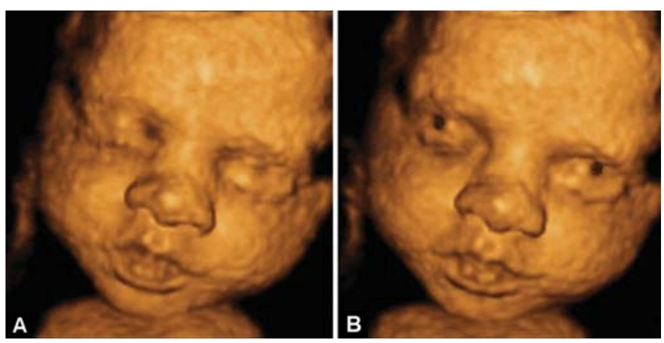
It is known that fetal movements occur much earlier than the time that mothers can feel them, even during the embryonic period.[26] The pattern, the quantity and the quality of fetal movements are growing rapidly throughout pregnancy, starting with gross, asynchronized movements of the whole embryo and 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] The first test that aimed to assess in a structured and systematic way the functional development of the CNS of the fetus, using 4D ultrasound was introduced about 5 years ago, and since then many multicenter studies have proved the usefulness of the test.[34] This new test was called Kurjak's antenatal neurodevelopment test (KANET), and one of its pioneering ideas is that it uses 4D ultrasound to assess the fetus *in utero*, in a similar way that neonates are examined postnatally for brain damage, incorporating parameters from neonatal neurological tests (Amiel-Tison), such as overlapping sutures of the skull and neurological thumb and some morphological dynamics, such as yawning, sucking, crying and blinking.[35-37] The aim of this review is to perform an extended literature research of all the studies involving KANET test and what this pioneering test has offered so far.

WHAT IS KANET?

Assessment of fetal and neonatal behavior was developed mainly as a diagnostic tool for the early detection of brain dysfunction.[1] KANET is a new scoring system for the assessment of fetal neurobehavior that 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] 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 month 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 third-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 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 (Figs 1 to 10).[38,39] 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 intraobservere variability 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 ten, 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



Figs 1A to F: Facial alterations and hand movements during Kurjak's antenatal neurodevelopmental test assessment



Figs 2A and B: Eye blinking

Fig. 3: Face grimacing

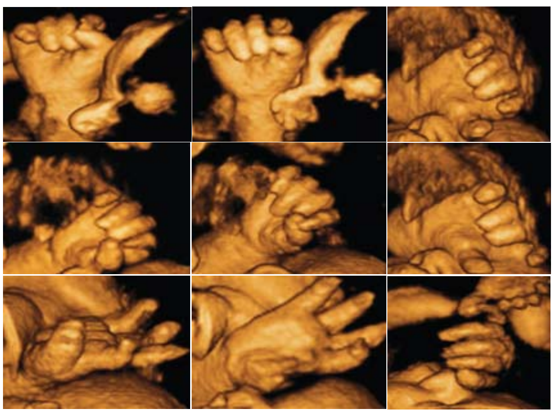


Fig. 4: Hand movements

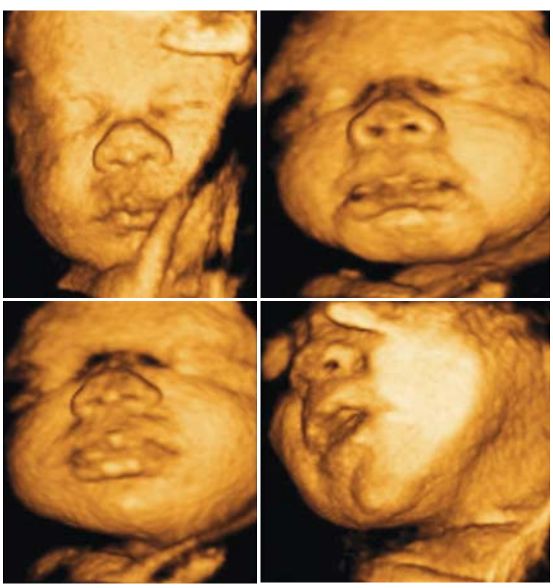


Fig. 5: Head anteflexion

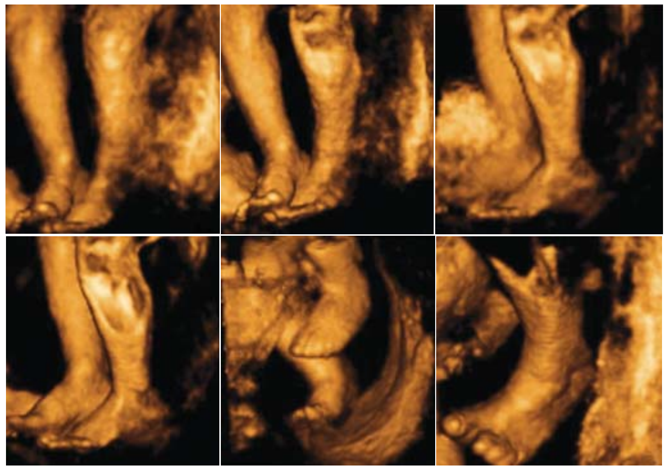


Fig. 6: Leg movements

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.

ADVANTAGES OF KANET

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 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

Fig. 7: Kurjak's antenatal neurodevelopmental test—facial alterations and head anteflexion

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]

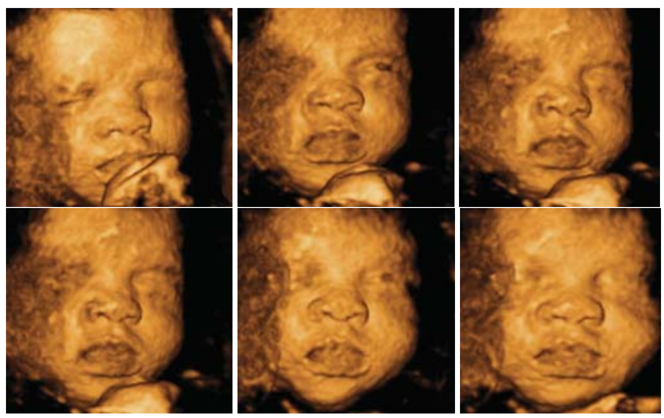


Fig. 8: Kurjak's antenatal neurodevelopmental test—eye blinking

RESULTS OF KANET: THE FIRST 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 third 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

Fig. 9: Kurjak's antenatal neurodevelopmental test—facial alterations and mouthing

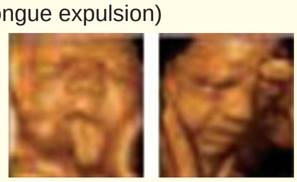
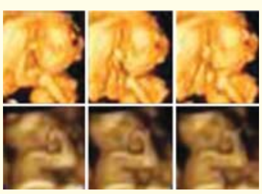
Fig. 10: Kurjak's antenatal neurodevelopmental test—facial alterations mouthing, eye blinking and hand movement

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 0-5. Among this group four had alobar holoprosencephaly, one had severe hypertensive hydrocephaly, one had than atotrophic 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,

Table 2: Proposal for the new Kurjak's antenatal neurodevelopmental test assessment tool consisting of eight parameters[41]

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 or above 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 alteration (>5 times of movements)	
Isolated hand movement 	Cramped or abrupt	Poor repertoire or small in range (0-5 times of movement)	Variable in full range, many alteration (>5 times of movements)	

Contd...

Contd...

Sign	*Score*			*Sign score*
	0	*1*	*2*	
or hand to face 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	

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, 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 with the results of the ATNAT tests, and found statistically significant difference among the low- and the high-risk groups, for eight out of the ten KANET parameters (isolated anteflexion of the head, eye blinking, facial expressions–grimacing, tongue expulsion, mouth movement 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]

Table 3: Interpretation of Kurjak's antenatal neurodevelopmental test scores[41]

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

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 diabetexs, intrauterine growth restriction, polyhydramnios, Rhesus isoimmunization, placental bleeding and maternal fever >39°C. Analysis of

Table 4: List of studies that have applied Kurjak's antenatal neurodevelopmental test to different population

Authors	Years	Study	Study design	Study population	Indication	No	GA (weeks)	Time	Result	Summary
Kurjak et al[34]	2008	Cohort	Retrospective	High-risk	Multiple	220	20-36	30	Positive	A new scoring system for the assessment of neurological status of fetuses, for antenatal application was proposed, based on retrospective observations
Kurjak et al[48]	2010	Multicenter	Prospective	High-risk	Multiple	288	20-38	30	Positive	KANET showed potential for antenatal detection of serious neurological fetal problems. KANET appeared to be able to identify serious structural abnormalities associated with brain impairment
Miskovic et al[52]	2010	Cohort	Prospective	High-risk	Multiple	226	20-36	30	Positive	Statistically significant moderate correlation of KANET and ATNAT tests was found. KANET confirmed the differences of fetal behavior between the high-risk and normal pregnancies
Talic et al[51]	2011	Multicenter cohort	Prospective	High-risk	Multiple	620	26-38	15-20	Positive	KANET test showed a potential of detection and discriminate normal from borderline and abnormal fetal behavior in normal and in high-risk fetuses. Low KANET scores were predictable of either intrauterine or postnatal death
Talic et al[54]	2011	Multicenter cohort	Prospective	High-risk	Ventriculo-megaly	240	32-36	10-15	Positive	KANET in normal pregnancies and pregnancies with ventriculomegaly showed statistically significant differences. Abnormal KANET scores and most of the borderline scores were found among the fetuses with severe ventriculomegaly associated with additional abnormalities
Honemeyer et al[60]	2011	Cohort	Prospective	Unselected	Unselected	100	28-38	N/A	Positive	Normal prenatal KANET scores were significantly predictive for normal postnatal neurological assessment of newborns
Lebit et al[27]	2011	Cohort	Prospective	Low-risk	Normal 2D examination	144	7-38	15-20	Positive	A pattern of fetal behavior for each trimester of pregnancy was identified
Abo-Yaqoub et al[50]	2012	Cohort	Prospective	High-risk	Multiple	80	20-38	15-20	Positive	The difference in KANET score was significant. All cases with abnormal KANET proved to be abnormal postnatally
Vladareanu et al[61]	2012	Cohort	Prospective	High-risk	Multiple	196	24-38	N/A	Positive	Most fetuses with normal KANET were low risk, those with borderline were IUGR fetuses with increased MCA RI and most fetuses with abnormal KANET were threatened PTD with PPROM. There were statistical significant difference fetal movements in the 2 groups. In normal pregnancies, most fetuses (93.4%) achieved a normal KANET score compared with 78.5% of the fetuses from high-risk pregnancies
Honemeyer et al[62]	2012	Cohort	Prospective	High and low risk	Multiple	56	28-38	30 max	Positive	Introduction of the average KANET score, which derived from the mean value of total KANET score during pregnancy showed connection of fetal diurnal rhythm with pregnancy risk

KANET: Kurjak's antenatal neurodevelopmental test; No: Number of patients; IUGR: Intrauterine growth restriction; MCA: Middle cerebral artery; PTD: Preterm delivery; PPROM: Preterm premature rupture of membranes 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 3 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 CNS 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 venticulomegaly and 100 normal fetuses. A total of 6% 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 CNS 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 with 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 Rhesus 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]

Many multicenter studies are currently running in different units all over the world, aiming to extensively study the application of the KANET scoring system for the assessment of fetal behavior and the benefits that the test offers. The first results seem to be very promising and this new pioneering method appears to finally give answers to the everlasting problem of assessing functional development of the fetal nervous system. Hopefully, future results of the prospective studies that are taking place at the moment will verify the promising results of the preliminary studies and further strengthen the evidence that KANET can identify functional characteristics of the fetus that predict normal and abnormal neurological development.

CONCLUSION

One of the greatest challenges of obstetrical ultrasonography is the better understanding of fetal neurological function.[37,63] Neurological problems such as CP, which has for many years been a huge scientific and medicolegal problem for obstetricians, is poorly understood and often is falsely attributed to intrapartum events, while for the majority of CP cases this is not true.[64-66] So the question of how could we define normal and abnormal fetal neurological function *in utero*, both for low-risk fetuses and fetuses at risk for neurological problems, irrespective of intrapartum management, has been one of the great obstetrical problems and has remained unanswered for many years.[65-67] Indeed, assessment of the integrity of the fetal nervous system is a major task in modern perinatal medicine.[48]

It is well-established that fetal behavioral patterns are directly reflecting developmental and maturational processes of fetal CNS.[65-67] It has been suggested that the assessment of fetal behavior and developmental processes in different periods of gestation may make possible the distinction between normal and abnormal brain development, as well as early diagnosis of various structural or functional abnormalities.[19] The innovation in fetal imaging, which enabled the study of fetal activity in explicit detail, was made by the introduction of high-quality 3D and 4D ultrasound (3D and 4D), which allowed the performance of real-time observation of the fetus, with sufficient dynamics and good image resolution, allowing the evaluation of even the face and small anatomic parts of the fetus, and especially the movements of the mouth, eyes (facial expressions) and fingers.[68-71] The first test that succeeded to combine all these parameters 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, in order to determine their neurological status during the first days of their life, is the KANET.[33] KANET has already been shown to be useful in standardization of neurobehavioral assessment with the potential for antenatal detection of fetuses with severe neurobehavioral impairment.[26,46,49] KANET has also succeeded to verify the good neurological outcomes of fetuses that had normal KANET scores, showing a great positive predictive value and offering reassurance for the neurological outcome of these pregnancies.[27,59] The first results prove that the prenatal neurological findings as estimated by KANET test, are in concordance with their postnatal outcome.[48] Of course, more studies are required to draw safe conclusions. Of great importance on this issue was the standardization of the test in order to be made reproducible and more easily applied, according to the Osaka Consensus Statement, during the International Symposium on Fetal Neurology of the International Academy of Perinatal Medicine (24th of October 2010).[41] The importance of postnatal follow-up was also emphasized, especially in infants with abnormal or borderline KANET. Following the suggestions of the Osaka consensus statement on the standardization of the method, the KANET can be introduced in everyday clinical practice as a reproducible and sensitive prenatal screening neurological test, on which future studies can be designed. The results of these ongoing studies will investigate sensitivity, specificity, negative and positive predictive values, intraobserver and interobserver variability and reproducibility of the KANET, and these outcomes will form the base for the guidelines of fetal neurosonography and neurobehavior assessment.[72]

KANET appears to be a great diagnostic tool for obstetricians, in detecting fetal brain and neuro-developmental alterations, due to *in utero* brain impairment, that is inaccessible by any other method.[39] However, additional studies in large populations are needed before recommending the test in routine clinical practice. The results from the first studies on KANET are very optimistic and new results from bigger, ongoing multicenter studies in universities all over the world, will be available soon and hopefully will verify what we have learned so far from KANET, and will help us to draw safe conclusions and valuable information for the prediction of fetal neurodevelopmental outcome. 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.

REFERENCES

1. Yigiter AB, Kavak ZN. Normal standards of fetal behavior assessed by four-dimensional sonography. J Matern Fetal Neonatal Med 2006 Nov;19(11):707-21.
2. Rees S, Harding R. Brain development during fetal life: Influences of the intra-uterine environment. Neurosci Lett. 2004 May 6;361(1-3):111-14.
3. Joseph R. Fetal brain and cognitive development. Dev Rev 1999;20:81-98.
4. Kurjak A, Carrera JM, Stanojevic M, Andonotopo W, Azumendi G, Scazzocchio E, et al. The role of 4D sonography in the neurological assessment of early human development. Ultrasound Rev Obstet Gynecol 2004 Sep;4(3):148-59.
5. Eidelman AI. The living fetus dilemmas in treatment at the edge of viability. In: Blazer S, Zimmer EZ (Eds). The embryo: Scientific discovery and medical ethics. Basel: Karger; 2005;351-70.
6. Stanojevic M, Zaputovic S, Bosnjak AP. Continuity between fetal and neonatal neurobehavior. Semin Fetal Neonatal Med 2012 Jul 16 [Epub ahead of print].
7. Haak P, Lenski M, Hidecker MJ, Li M, Paneth N. Cerebral palsy and aging. Dev Med Child Neurol 2009 Oct;51(Suppl 4):16-23.
8. Einspieler C, Prechtl HF. Prechtl's assessment of general movements: A diagnostic tool for the functional assessment of the young nervous system. Ment Retard Dev Disabil Res Rev 2005;11(1):61-67.
9. Salihagic-Kadic A, Kurjak A, Mediæ M, Andonotopo W, Azumendi G. New data about embryonic and fetal neurodevelopment and behavior obtained by 3D and 4D sonography. J Perinat Med 2005;33(6):478-90.
10. Moster D, Wilcox AJ, Vollset SE, Markestad T, Lie RT. Cerebral palsy among term and postterm births. JAMA 2010 Sep 1;304(9):976-82.
11. Almli CR, Ball RH, Wheeler ME. Human fetal and neonatal movement patterns: Gender difference and fetal-to-neonatal continuity. Dev Psychobiol 2001;38:252-73.
12. DiPietro JA, Bronstein MH, Costigan KA, Pressmen EK, Hahn CS, Painter K, et al. What does fetal movement predict about behavior during the first two years of life? Dev Psychobiol 2002 May;40(4):358-71.
13. DiPetro JA, Hodson DM, Costigan KA, Johnson TR. Fetal antecedents of infant temperament. Child Dev 1996 Oct;67(5):2568-83.
14. DiPietro JA, Costigan KA, Pressman EK. Fetal state concordance predicts infant state regulation. Early Hum Dev 2002 Jun;68(1):1-13.
15. Thoman EB, Denenberg VH, Sievel J, Zeidner LP, Becker P. State organization in neonate: Developmental inconsistency indicates risk for developmental dysfunction. Neuropediatrics 1981 Feb;12(1):45-54.

16. St James-Roberts I, Menon-Johansson P. Predicting infant crying from fetal movement data: An exploratory study. Early Hum Dev 1999 Feb;54(1):55-62.
17. Einspieler C, Prechtl HF, Ferrari F, Cioni G, Bos AF. The qualitative assessment of general movements in preterm, term and young infants-review of the methodology. Early Hum Dev 1997 Nov;50(1):47-60.
18. Precht HF. Qualitative changes of spontaneous movements in fetus and preterm infant are a marker of neurological dysfunction. Early Hum Dev 1990 Sep;23(3):151-58.
19. de Vries JI, Visser GH, Prechtl HF. The emergence of fetal behaviour. II. Quantitative aspects. Early Hum Dev 1985 Nov;12(2):99-120.
20. de Vries JI, Visser GH, Prechtl HF. The emergence of fetal behaviour. III. Individual differences and consistencies. Early Hum Dev 1988 Jan;16(1):85-103.
21. de Vries JI, Visser GH, Prechtl HF. The emergence of fetal behaviour. I. Qualitative aspects. Early Hum Dev 1982 Dec;7(4):301-22.
22. Nijhuis JG (Ed). Fetal Behaviour: Developmental and perinatal aspects. Oxford: Oxford University Press 1992.
23. Prechtl HF. State of the art of a new functional assessment of the young nervous system. An early predictor of cerebral palsy. Early Hum Dev 1997 Nov;50(1):1-11.
24. Kurjak A, Luetic AT. Fetal neurobehavior assessed by three-dimensional/four dimensional sonography. Zdrav Vestn 2010;79:790-99.
25. Salihagic - Kadic A, Medic M, Kurjak A, et al. 4D sonography in the assessment of fetal functional neurodevelopment and behavioural paterns. Ultrasound Rev Obstet Gynecol 2005; 5:1-15.
26. Kurjak A, Pooh R, Tikvica A, et al. Assesment of fetal neurobehavior by 3D/4D ultrasound. Fetal Neurology 2009: 222-50.
27. Lebit DF, Vladareanu PD. The role of 4D ultrasound in the assessment of fetal behaviour. Maedica (Buchar) 2011 Apr;6(2):120-27.
28. Merz E, Abramowicz JS. 3D/4D ultrasound in prenatal diagnosis: Is it time for routine use? Clin Obstet Gynecol 2012 Mar;55(1):336-51.
29. Kurjak A, Vecek N, Hafner T, Bozek T, Funduk-Kurjak B, Ujevic B. Prenatal diagnosis: What does four-dimensional ultrasound add? J Perinat Med 2002;30(1):57-62.
30. Kurjak A, Vecek N, Kupesic S, Azumendi G, Solak M. Four dimensional ultrasound: How much does it improve perinatal practice? In: Carrera JM, Chervenak FA, Kurjak A (Eds). Controversies in perinatal medicine: Studies on the fetus as a patient. New York: CRC Press (Parthenon Publishing) 2003;222.
31. Andonotopo W, Stanojevic M, Kurjak A, Azumendi G, Carrera JM. Assessment of fetal behavior and general movements by four-dimensional sonography. Ultra Rev Obstet Gynecol 2004;4(2):103-08.
32. Kurjak A, Carrera J, Medic M, Azumendi G, Andonotopo W, Stanojevic M. The antenatal development of fetal behavioral patterns assessed by four-dimensional sonography. J Matern Fetal Neonatal Med 2005 Jun;17(6):401-16.
33. Kurjak A, Tikvica A, Stanojevic M, Miskovic B, Ahmed B, Azumendi G, et al. The assessment of fetal neurobehavior by three-dimensional and four-dimensional ultrasound. J Matern Fetal Neonatal Med 2008Oct;21(10):675-84.
34. Kurjak A, Miskovic B, Stanojevic M, Amiel-Tison C, Ahmed B, Azumendi G, et al. New scoring system for fetal neurobehavior assessed by three- and four-dimensional sonography. J Perinat Med 2008;36(1):73-81.
35. 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(1):34-51.
36. 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(6):437-46.
37. Tomasovic S, Predojevic M. 4D Ultrasound—medical devices for recent advances on the etiology of cerebral palsy. Acta Inform Med 2011;19(4):228-34.
38. Kurjak A, Andonotopo W, Hafner T, Salihagic Kadic A, Stanojevic M, et al. Normal standards for fetal neurobehavioral developments—longitudinal quantification by four-dimensional sonography. J Perinat Med 2006;34(1):56-65.
39. Kurjak A, Stanojevic M, Andonotopo W, Scazzocchio-Duenas E, Azumendi G, Carrera JM. Fetal behavior assessed in all three trimesters of normal pregnancy by four-dimensional ultrasonography. Croat Med J 2005 Oct;46(5):772-80.
40. Stanojevic M, Kurjak A, Salihagic-Kadic A, et al. Neurobehavioral continuity from fetus to neonate. J Perinat Med 2011;39:171-77.
41. Stanojevic M, Talic A, Miskovic B, Vasilj O, Shaddad AN, Ahmed B, et al. An attempt to standardize kurjak's antenatal neurodevelopmental test: Osaka consensus statement. Donald School J Ultrasound Obstet Gynecol 2011 Oct-Dec;5:317-29.
42. Pooh RK, Pooh K, Fetal VM. Donald School J Ultrasound Obstet Gynecol 2007 Oct-Dec1(4):40-46.
43. Kurjak A, Ahmed B, Abo-Yaquab S, Younis M, Saleh H, Shaddad AN, et al. An attempt to introduce neurological test for fetus based on 3D and 4D sonography. Donald School J Ultrasound Obstet Gynecol 2008;2:29-44.
44. Kuno A, Akiyama M, Yamashiro C, Tanaka H, Yanagihara T, Hata T. Three-dimensional sonographic assessment of fetal behavior in the early second trimester of pregnancy. J Ultrasound Med 2001 Dec;20(12):1271-75.
45. Koyanagi T, Horimoto N, Maeda H, Kukita J, Minami T, Ueda K, et al. Abnormal behavioral patterns in the human fetus at term: Correlation with lesion sites in the central nervous system after birth. J Child Neurol 1993 Jan;8(1):19-26.
46. Kurjak A, Stanojevic M, Andonotopo W, Salihagic-Kadic A, Carrera JM, Azumendi G. Behavioral pattern continuity from prenatal to postnatal life—a study by four-dimensional (4D) ultrasonography. J Perinat Med 2004;32(4):346-53.
47. Stanojevic M, Kurjak A. Continuity between fetal and neonatal neurobehavior, Donald School J Ultrasound Obstet Gynecol 2008;2:64-75.
48. Kurjak A, Abo-Yaqoub S, Stanojevic M, Yigiter AB, Vasilj O, Lebit D, et al. The potential of 4D sonography in the assessment of fetal neurobehavior—multicentric study in high-risk pregnancies. J Perinat Med 2010;38(1):77-82.
49. Andonotopo W, Kurjak A, Kosuta MI. Behavior of an anencephalic fetus studied by 4D sonography. J Matern Fetal Neonatal Med 2005 Feb;17(2):165-68.
50. Abo-Yaqoub S, Kurjak A, Mohammed AB, Shadad A, Abdel-Maaboud M. The role of 4D ultrasonography in prenatal assessment of fetal neurobehaviour and prediction of

neurological outcome. J Matern Fetal Neonatal Med 2012 Mar;25(3):231-36.
51. Talic A, Kurjak A, Ahmed B, Stanojevic M, Predojevic M, Kadic AS, et al. The potential of 4D sonography in the assessment of fetal behavior in high-risk pregnancies. J Matern Fetal Neonatal Med 2011 Jul;24(7):948-54.
52. Miskovic B, Vasilj O, Stanojevic M, Ivankoviæ 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 Dec;23(12):1461-67.
53. Andonotopo W, Kurjak A. The assessment of fetal behavior of growth restricted fetuses by 4D sonography. J Perinat Med 2006;34(6):471-78.
54. Talic A, Kurjak A, Stanojevic M, Honemeyer U, Badreldeen A, Direnzo GC. The assessment of fetal brain function in fetuses with ventrikulomegaly: The role of the KANET test. J Matern Fetal Neonatal Med 2012;25(8):1267-72.
55. Kurjak A, Miskovic B, Andonotopo W, Stanojevic M, Azumendi G, Vrcic H. How useful is 3D and 4D ultrasound in perinatal medicine? J Perinat Med 2007;35(1):10-27.
56. Horimoto N, Koyanagi T, Maeda H, Satoh S, Takashima T, Minami T, et al. Can brain impairment be detected by in utero behavioural patterns? Arch Dis Child 1993 Jul;69(1 Spec No):3-8.
57. Morokuma S, Fukushima K, Yumoto Y, Uchimura M, Fujiwara A, Matsumoto M, et al. Simplified ultrasound screening for fetal brain function based on behavioral pattern. Early Hum Dev 2007 Mar;83(3):177-81.
58. Prechtl HF, Einspieler C. Is neurological assessment of the fetus possible? Eur J Obstet Gynecol Reprod Biol 1997 Dec;75(1): 81-84.
59. Nijhuis JG, Prechtl HF, Martin CB, Bots RS. Are there behavioral states in the human fetus? Early Hum Dev 1982;6:177-95.
60. Honemeyer U, Kurjak A. The use of KANET test to assess fetal CNS function. First 100 cases. 10th World Congress of Perinatal Medicine 8-11 November 2011. Uruguay. Poster presentation. 209.
61. Vladareanu R, Lebit D, Constantinescu S. Ultrasound assessment of fetal neurobehaviour in high-risk pregnancies. DSJUOG April-June 2012;6(2):Q132-47.
62. Honemeyer U, Talic A, Therwat A, Paulose L, Patidar R. The clinical value of KANET in studying fetal neurobehavior in normal and at-risk pregnancies. J Perinat Med 2012 Sep 28;0(0):1-11.
63. Hepper PG. Fetal behavior: Who so sceptical? Ultrasound Obstet Gynecol 1996;8(3):145-48.
64. Greenwood C, Newman S, Impey L, Johnson A. Cerebral palsy and clinical negligence litigation: A cohort study. BJOG 2003 Jan;110(1):6-11.
65. Strijbis EM, Oudman I, van Essen P, MacLennan AH. Cerebral palsy and the application of the international criteria for acute intrapartum hypoxia. Obstet Gynecol 2006 Jun;107(6): 1357-65.
66. de Vries JI, Fong BF. Changes in fetal motility as a result of congenital disorders: An overview. Ultrasound Obstet Gynecol 2007 May;29(5):590-99.
67. de Vries JI, Fong BF. Normal fetal motility: An overview. Ultrasound Obstet Gynecol 2006 Jun;27(6):701-11.
68. Rosier-van Dunné FM, van Wezel-Meijler G, Bakker MP, de Groot L, Odendaal HJ, de Vries JI. General movements in the perinatal period and its relation to echogenicity changes in the brain. Early Hum Dev 2010 Feb;86(2):83-86.
69. Hata T, Kanenishi K, Akiyama M, Tanaka H, Kimura K. Real-time 3-D sonographic observation of fetal facial expression. J Obstet Gynaecol Res 2005 Aug;31(4):337-40.
70. Kozuma S, Baba K, Okai T, Taketani Y. Dynamic observation of the fetal face by three-dimensional ultrasound. Ultrasound Obstet Gynecol 1999Apr;13(4):283-84.
71. 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 2007Jan;196(1):16-28.
72. Kurjak A, Predojevic M, Kadic AS. Fetal brain function: Lessons learned and future challenges of 4D sonography. Donald School J Ultrasound Obstet Gynecol 2010 (April-June 2011);2(5): 85-92.

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