The Assessment of Fetal Neurobehavior with 4D Ultrasound: the KANET Test

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ABSTRACT

An evolving challenge for obstetrician is to better define normal and abnormal fetal neurological function in utero, in order to better predict antenatally which fetuses are at risk for adverse neurological outcome. Especially the diagnosis of cerebral palsy remains one of the most difficult and challenging clinical situations in obstetrics. The fact that a large number of cerebral damage occurs prenatally and also that early intervention in cases of neurological damage shows better results, in combination with the progression of ultrasound technology, which allows better and real time assessment of the fetus, prompted some researchers to explore the possibility of detecting fetal neurological damage in the uterus. Systematic estimation of a number of parameters from fetal behavior, such as quality of spontaneous fetal movements, cranial sutures, the neurological thumb and a high palate, that were included in the prenatal neurological fetal screening, led to formation of a scoring system for the assessment of fetal neurobehavior, called Kurjak’s antenatal neurodevelopmental test (KANET). The introduction of such a test allows a systematic assessment of fetal neurobehaviour and may distinguish between normal and abnormal behavioral patterns, that could make possible the early recognition of fetal brain impairment.

KEY WORDS

fetal neurology, 4D ultrasound

Introduction

The study of fetal nervous system has been a great challenge for obstetricians and neonatologists for many years [1-3]. The introduction of 2D ultrasound in obstetrics allowed direct visualization of fetal anatomy and 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 fetal neurosonography and in the study of fetal behavior in utero [4]. It has been suggested that fetal behavioral patterns directly reflect developmental and maturation processes of fetal nervous system, and that assessment of fetal behavior during different periods of gestation could make it possible to distinguish between normal and abnormal brain development [4-6]. 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 [7-9]. However, 2D ultrasound with poor quality images was considered to be somewhat subjective, because the information needed observer’s interpretation [6]. These problems could be overcome with 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 us with better pictures and real time images that help us 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 [10]. Studies have shown that 4D ultrasound offers a practical mean of assessment of both brain anatomy and function, with more details and much earlier than 2D ultrasound [11]. What is more, 4D ultrasound, by obtaining real time images, allows spatial observations of fetal face, which 2D ultrasound does not, and multicenter studies have verified that with 4D ultrasound it is feasible to distinguish between normal and abnormal behavioral patterns, which could lead to early diagnosis of fetal brain impairment [12]. The advantages of three and four dimensional ultrasound in the assessment of fetal anatomy and fetal behavior, has been shown by large studies [35]. It is known that fetal movements occur much earlier than the time that mothers can feel them, even during the embryonic period [13]. 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 and facial expressions, towards the end of the pregnancy [14]. The first test that aimed to assess in a structured and systematic way the functional
development of the central nervous system 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 [15]. This new test was called Kurjak’s antenatal neurodevelopment test (KANET), and one of the pioneering ideas of the test 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 [16-18]. 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 (Figures 1-8).

Figure 1a-f: facial alterations and hand movements during KANET test assessment

Figure 2: eye blinking

What is Kurjak’s antenatal neurodevelopmental Test (KANET)

Kurjak’s antenatal neurobehavioral test (KANET) is a new scoring system for fetal neurobehavior, that has been recently introduced and is based on prenatal assessment of the fetus by 3D/4D ultrasound [15]. This scoring system is a combination of some parameters consisting of fetal general movements (GM) and of postnatal Amiel-Tison Neurological Assessment at Term (ATNAT) signs, which can be easily visualized prenatally by using 4D ultrasound [17,21]. The parameters were chosen based on developmental approach to the neurological assessment and on the theory of central pattern generators of general movements emergence, and were the product of multicentric studies conducted for several years [19-20]. The 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 [21]. 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 15-20 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 14-16 hours.

**Table-1: Proposal for the new KANET assessment tool consisting of eight parameters:**

<table>
<thead>
<tr>
<th>Sign</th>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated head movements</td>
<td>Absent</td>
<td>Small range (0-5 times of movements)</td>
<td>Variable in full range, many alternations (&gt; 3 times of movements)</td>
</tr>
<tr>
<td>Cranial amplitudes and head movements</td>
<td>Overlapping of cranial amplitudes</td>
<td>Normal cranial amplitudes with measurement of HC below or above the normal limit (1-2 SD) according to GA</td>
<td>Normal cranial amplitudes with normal measurement of HC according to GA</td>
</tr>
<tr>
<td>Isolated eye blinking</td>
<td>Not present</td>
<td>No fast (1-5 times of blinking)</td>
<td>Fluctuance (&gt; 5 times of blinking)</td>
</tr>
<tr>
<td>Facial movements (cheeks or tongue protrusion)</td>
<td>Not present</td>
<td>No fast (1-5 times of movement)</td>
<td>Fluctuance (&gt; 5 times of movement)</td>
</tr>
<tr>
<td>Isolated leg movements</td>
<td>Cramped</td>
<td>Poor repetition or fixed sequence (0-5 times of movement)</td>
<td>Variable in full range, many alternations (&gt; 3 times of movements)</td>
</tr>
<tr>
<td>Cramped or absent</td>
<td>Poor repetition or fixed sequence (0-5 times of movement)</td>
<td>Variable in full range, many alternations (&gt; 3 times of movements)</td>
<td></td>
</tr>
<tr>
<td>Pelvis movements</td>
<td>Unilateral or bilateral (directed fat, mesocolic folds)</td>
<td>Complicated variable finger movements</td>
<td>Search and complex, unstable finger movements</td>
</tr>
<tr>
<td>Head to face movements</td>
<td>Definitely abnormal</td>
<td>Borderline</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**Table-2: Interpretation of KANET scores:**

<table>
<thead>
<tr>
<th>TOTAL SCORE</th>
<th>INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>Abnormal</td>
</tr>
<tr>
<td>6-9</td>
<td>Borderline</td>
</tr>
<tr>
<td>10-16</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**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 non-ultrasonic methods, enabling to observe fetal movements in their full repertoire and variability. The parameters examined by this test are partly based on observation of general movements (GMs). A second group of parameters is adopted from Amiel Tison Neurological assessment at term (ATNAT) [22-23]. The criterion of quality and quantity of spontaneous GMs is believed to have excellent reliability in evaluating the integrity of fetal CNS [4, 24]. Furthermore a continuity of behavioral patterns from prenatal to the postnatal period has been proven [25-27]. 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 [28-33] 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 [34]. 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 [36-39]. 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 15-20 minutes, showing strong evidence that it can be widely implemented for fetal neurological assessment [32]. 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 [21].

**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 IUGR fetuses in the 3rd trimester of pregnancy, a tendency of less behavioural 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 behaviour as possible indicators of the neurological condition in IUGR fetuses [33].

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 in 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 14-20, 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 14-20. Ten fetuses who were postnatally described as mildly or moderately abnormal achieved a prenatal score of 5-13, while another ten fetuses postnatally assigned as neurologically abnormal had a prenatal score 0-5. Among this group four had alobar holoprosencephally, one had severe hypertensive hydrocephaly, one had thanatotrophic dysplasia and four fetuses had multiple malformations. This study inspired a large series of multicenter studies (Table-3) 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 [6,15].

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. 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 had verified cerebral palsy. 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 and having a very low KANET score. The authors reached the conclusion that there is a potential for antenatal detection of serious neurological conditions [28].

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 for eight out of ten KANET parameters, among the low and the high risk groups. Comparison of KANET and ATNAT showed statistically significant, moderate correlation between the two tests, which means that the neuropaediatric exam (ATNAT) confirmed the prenatal findings of 4D US (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 [32].
Table 3: List of studies that have applied KANET test to different populations

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Study Population</th>
<th>Indication</th>
<th>No.</th>
<th>GA (weeks)</th>
<th>Time (mins)</th>
<th>Result</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurjak et al. [15]</td>
<td>2008</td>
<td>Cohort</td>
<td>Retrospective</td>
<td>High-Risk</td>
<td>220</td>
<td>20-36</td>
<td>30</td>
<td>Positive</td>
<td>A new scoring system for the assessment of neurological status of fetuses, for antenatal application was proposed, based on retrospective observations</td>
</tr>
<tr>
<td>Kurjak et al. [28]</td>
<td>2010</td>
<td>Multicenter</td>
<td>Prospective</td>
<td>High-Risk</td>
<td>288</td>
<td>20-38</td>
<td>30</td>
<td>Positive</td>
<td>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</td>
</tr>
<tr>
<td>Miskovic et al. [32]</td>
<td>2010</td>
<td>Cohort</td>
<td>Prospective</td>
<td>High-Risk</td>
<td>226</td>
<td>20-36</td>
<td>30</td>
<td>Positive</td>
<td>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</td>
</tr>
<tr>
<td>Talic et al. [31]</td>
<td>2011</td>
<td>Multicenter</td>
<td>Cohort</td>
<td>High-Risk</td>
<td>620</td>
<td>26-38</td>
<td>15-20</td>
<td>Positive</td>
<td>KANET test showed a potential of detection and discriminate normal from border line and abnormal fetal behavior in normal and in high risk fetuses. Low KANET scores were predictable of either intrauterine or postnatal death.</td>
</tr>
<tr>
<td>Talic et al. [29]</td>
<td>2011</td>
<td>Multicenter</td>
<td>Cohort</td>
<td>High-Risk</td>
<td>240</td>
<td>32-36</td>
<td>10-15</td>
<td>Positive</td>
<td>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</td>
</tr>
<tr>
<td>Honemeyer et al. [40]</td>
<td>2011</td>
<td>Cohort</td>
<td>Prospective</td>
<td>Unselected</td>
<td>100</td>
<td>28-38</td>
<td>N/A</td>
<td>Positive</td>
<td>Normal prenatal KANET scores were significantly predictive for normal postnatal neurological assessment of newborns</td>
</tr>
<tr>
<td>Lebit et al. [14]</td>
<td>2011</td>
<td>Cohort</td>
<td>Prospective</td>
<td>Low-risk</td>
<td>144</td>
<td>7-38</td>
<td>15-20</td>
<td>Positive</td>
<td>A pattern of fetal behavior for each trimester of pregnancy was identified</td>
</tr>
<tr>
<td>Abo-Yaqoub et al. [35]</td>
<td>2012</td>
<td>Cohort</td>
<td>Prospective</td>
<td>High-Risk</td>
<td>80</td>
<td>20-38</td>
<td>15-20</td>
<td>Positive</td>
<td>The difference in KANET score was significant. All cases with abnormal KANET proved to be abnormal postnataally</td>
</tr>
</tbody>
</table>

KANET: Kurjak’s antenatal neurological test, No: number of patients

Talic et al around the same period, in a multicenter study, published the largest series of KANET so far, with 620 singleton pregnancies, both normal and high risk, excluding however fetuses with structural abnormalities. 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 cerebral palsy (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 general movements. The authors observed that a low KANET score is predictive of both intrauterine or neonatal death – had two intrauterine deaths in
fetuses with low KANET (3 and 4 respectively) and one neonatal death (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. Other neonates are still followed up in this study, in order to reach safe conclusions [31].

Honemeyer et al studied 100 fetuses, who underwent, between 28-38 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 [40].

Lebit et al used part of the KANET to assess fetal movements throughout pregnancy in 144 low risk pregnancies, between 7-38 weeks of gestation, concluding to a specific pattern of fetal behavior for each trimester of pregnancy [14]. 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 [7,13]. 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 [14].

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 32-36 weeks of gestation, 140 fetuses with ventriculomegaly and 100 normal fetuses. 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. 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. Also the degree of ventriculomegaly and the presence of coexisting congenital malformations, appeared to be important factors determining the final KANET score [29]. 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.

More recently, Abo-Yaqoub et al studied forty pregnant women between 20 and 38 weeks of gestation with high risk for neurological abnormalities using KANET scoring system and compared the results with 40 low risk cases. The difference in the range of KANET score was significant between the 2 groups. All cases with abnormal KANET proved to be abnormal postnatally [30].

Many multicentre 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 behaviour, 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 [17, 41]. Neurological problems such as cerebral palsy, 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 cerebral palsy cases this is not true [42-43]. 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 [44-45]. Indeed, assessment of the integrity of the fetal nervous system is a major task in modern perinatal medicine [28].

It is well established that fetal behavioral patterns are directly reflecting developmental and maturational processes of fetal central nervous system [44-46]. 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 [4]. The innovation in fetal imaging, which enabled the study of fetal activity in explicit detail, was made by the introduction of high quality three and four dimensional ultrasound (3D & 4D), which allowed the performance of real time observation of the fetus, with sufficient dynamics and good image resolution, enabling 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 [47-49]. 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 Kurjak antenatal neurodevelopmental test (KANET) [15].

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 [15, 28, 31]. 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 [9, 40]. The first results prove that the prenatal neurological findings as estimated by KANET test, are in concordance with their postnatal outcome [29]. 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) [21]. 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 [50].

KANET appears to be a great tool for obstetricians, in detecting fetal brain and neurodevelopmental alterations, due to in utero brain impairment, that is inaccessible by any other method [23]. 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 cerebral palsy and also provide valuable evidence for cases of litigation.

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