

Recent Results of the Clinical Application of KANET Test

¹Raul Moreira Neto, ²Asim Kurjak

ABSTRACT

Many investigations led to the conclusion that fetal behavioral patterns directly reflect developmental and maturational processes of fetal central nervous system (CNS), and may make possible to distinguish between normal and abnormal brain development as well as prenatal diagnosis of neurological impairment. The arrival of three- and four-dimensional ultrasound (3D/4D US) made possible to study fetal behavioral patterns. Kurjak's antenatal neurodevelopmental test (KANET) is the first prenatal test based on 3D/4D ultrasound examination of the fetus, that could be used for the evaluation and prediction of fetal neurological status. Here, we present our review of literature on KANET around the world and summarized results of this promising prenatal neurological screening test.

Keywords: Fetal behavior, Fetal neurologic screening, Kurjak's antenatal neurodevelopmental test, Neurobehavioral development, Neurodevelopment, Postnatal assessment, Prenatal assessment, Prenatal brain impairment, Three/four-dimensional ultrasound.

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INTRODUCTION

The study of fetal nervous system has been a major challenge for obstetricians and neonatologists for many years.¹⁻³ The detection and prevention of early neurological damage is one of the most important tasks of perinatal medicine. The analysis of fetal behavior dynamics led to the conclusion that patterns of intrauterine behavior directly reflect the processes of development and maturation of fetal central nervous system (CNS). This behavioral analysis made it possible to distinguish between normal and abnormal brain development and early diagnosis of various abnormalities.⁴⁻⁶

Cerebral palsy (CP) is the disease that causes most of childhood chronic motor disabilities. Worldwide prevalence is around 2 to 4 per 1000 live births, with incidence unchanged since 1951.⁹ The specificity of the diagnosis increases with child growth and subsequent brain maturity. The traditional concept that brain damage is caused during birth or in early neonatal period is changing. Currently, the prenatal stage is considered the most important etiologic factor to brain damage, as clinical and epidemiological studies have shown.¹⁰⁻¹²

Fetal movements begin during the embryonic period much earlier than mothers can feel them.⁷ They grow rapidly in pattern, quantity and quality throughout pregnancy, starting with gross and unsynchronized embryo movements, evolving gradually to coordinated movements, such as single finger movement and facial expression.⁸

Four-dimensional ultrasound (4D US) provides a practical mean for the evaluation of both brain function and structure. The analysis of fetal activity *in utero* by 4D ultrasound may allow early diagnosis of fetal neurological deficiencies.^{7,14,24} This new technology enabled the introduction of a test, called KANET (Kurjak's antenatal neurodevelopmental test) for evaluation of high-risk pregnancies. This new test shows a relationship between fetal behavior and neurodevelopmental processes in different periods of pregnancy, making it possible to distinguish between normal and abnormal brain development.¹⁹

FOUR-DIMENSIONAL ULTRASOUND

The arising of 4D technology for ultrasound machines could promote fetal behavioral studies. In contrast with 2D ultrasound, fetal 4D display provides better real time images that analyzes its anatomy, movements and behavior more accurately and earlier.⁶⁻⁸

During the last 12 years, Zagreb group (Kurjak et al) have been doing an extensive research on fetal behavior in normal and pathological pregnancies, both by three and four-dimensional ultrasound.^{6-8,19-22,24,33,62,63} The objective was to identify normal patterns of fetal movements and facial expressions.

ABOUT KANET

Kurjak's antenatal neurodevelopmental test is the first test that evaluates functional development of

¹Professor and Director, ²Emeritus Professor

¹Department of Fetal Medicine, Ecomoinhos—School and Clinic of Ultrasonography, Porto Alegre, Brazil

²Department of Obstetrics and Gynecology, University of Zagreb Zagreb, Croatia

Corresponding Author: Raul Moreira Neto, Professor and Director, Department of Fetal Medicine, Ecomoinhos—School and Clinic of Ultrasonography, Rua Tobias da Silva 120/502, Porto Alegre, RS, Brazil, CEP 90570-020, e-mail: raul@ecomoinhos.com.br

fetal CNS using 4D US, in a structured and systematic way, being introduced some time ago.⁶⁴ Since then, many multicenter studies have proven its usefulness.^{8,13,15-17,23,26-32,34-40,45,46,57,60} This exam is a pioneer idea that uses 4D US to access fetal movements and facial expression, similar to neonatal neurological tests, such as a test called ATNAT (Amiel-Tison Neurological Assessment at Term).^{19,41,42,62,64-66}

Kurjak's antenatal neurodevelopmental test has the potential to detect and discriminate normal, borderline and abnormal fetal behavior in high-risk pregnancies, it can, therefore, become a valuable diagnostic tool for fetal neurological assessment. In order to make the test reproducible and easy to apply for fetal medicine specialists, it was proposed its standardization in 2010, which was widely accepted. This took place in Osaka, Japan, during the International Symposium on Fetal Neurology from the International Academy of Perinatal Medicine.⁴⁴

So far, KANET has proven its usefulness in standardization of neurobehavioral assessment, with the potential for prenatal detection of fetuses with severe neuronal dysfunction. Other researches are being conducted in various centers with similar objectives: to evaluate the practical clinical application of the test in normal and high-risk pregnancies. Components of KANET and its resulting scores are shown elsewhere.¹³ Kurjak's antenatal neurodevelopment test should be performed in third trimester, after 28 weeks of pregnancy, because cortical maturation process start at this period. The scores range from 0 to 16. Zero to 5 is abnormal; 6 to 9 is borderline and 10 to 16 is normal.

KANET STUDIES RESULTS

One of the first studies to use an initial form of KANET scoring system was by Andonotopo and Kurjak in 2006. They evaluated fetal facial expressions and quality of body movements in fetuses with intrauterine growth restriction (IUGR) analyzing whether it was possible to diagnose brain impairment. After analyzing 50 pregnancies in the 3rd trimester, a trend of lower behavioral activity in fetuses with IUGR was noted. The study results encouraged further investigation of 4D US for quantitative and qualitative assessment of fetal behavior as possible indicators of neurological condition in fetuses with IUGR.¹⁹

In 2008, a group from Zagreb was the first to introduce KANET score to detect neurodevelopmental changes due to brain damage *in utero*. To develop the new scoring system, they first separated newborns with severe brain damage from those in good neurological condition;

afterward, the neonatal outcomes were compared to prenatal findings. This study inspired a large number of multicenter studies that used KANET to evaluate the usefulness of this promising new scoring system for assessment of neurological status in fetuses and recognition of early signs of cerebral impairment.⁴⁹

Results from 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. Three of these had an abnormal ATNAT score after birth. The authors concluded that there is a potential for the prenatal detection of serious neurological disorders.⁵⁵

Also in 2010, Miskovic et al applied KANET in 226 high- and low-risk pregnancies and compared the results. They found three cases of abnormal KANET with chromosomal abnormalities, which had also abnormal ATNAT. The KANET scores of both groups were compared with the results of ATNAT tests, finding statistically significant differences for eight out of 10 KANET parameters, between high- and low-risk groups.⁵⁶

Talic et al performed a multicenter study with the largest number of KANET tests so far, with 620 singleton pregnancies of low- and high-risk, excluding fetuses with structural abnormalities. Data analysis confirmed a statistically significant difference in the distribution of KANET points between the two populations. Twenty-four percent of pregnant women who had previous child with CP, had abnormal KANET during the current pregnancy. Authors also observed that a low KANET score is predictive of intrauterine and neonatal death. There were two intrauterine deaths in fetuses with low KANET and neonatal death score. Ten out of 36 fetuses with abnormal KANET had postnatal neurological evaluation after 2 and 6 months indicating seriously abnormal findings: four of them had severe generalized spasticity.⁴⁵

Honemeyer et al performed KANET test in 100 fetuses, with postnatal follow-up immediately after birth and at 12 weeks of age, with systematic neurological evaluation by a neonatologist. The results of pre- and postnatal scoring systems were compared, showing that normal prenatal KANET score is significantly predictive of the normal postnatal neurological examination of the newborn. The authors concluded that the scores of normal prenatal KANET are good predictor of a normal postnatal neurological outcome.⁵⁸

A different study by Talic et al in 2011 aimed to assess fetal behavioral differences in normal fetuses and those with cerebral ventriculomegaly, using KANET. They studied 240 fetuses between 32 and 36 weeks of pregnancy, 140 of them with ventriculomegaly. Of normal

fetuses, 6% had pathological KANET scores, as of fetuses with ventriculomegaly, this index rose to 35%. There were no fetuses with abnormal KANET in mild and moderate ventriculomegaly group. 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.⁵⁷

Lebit et al, in 2011, also make an assessment of fetal movements throughout the pregnancy using 4D ultrasound, to see the difference of patterns in the first, second and third trimesters. The study group included 144 healthy pregnant women with single pregnancies between 7 and 38 weeks of gestation. For the first trimester of pregnancy was assessed eight types of fetal movements and for the second and third trimesters 14 types of fetal movements and facial expressions were analyzed, always using KANET. They found a different pattern of fetal behavior for each trimester of pregnancy. They concluded that the identification of dynamic and static patterns of the symptoms may be helpful to date precisely the time when the insult occurs.⁶⁷

More recently, Abo-Yaqoub et al studied 40 patients between 20 and 38 weeks of high-risk pregnancy for neurological abnormalities using KANET scoring system and compared the results with 40 low-risk cases. The score difference was significant between the two groups. All cases with abnormal KANET proved to be abnormal postnatally.⁵⁹

Vladareanu et al, in 2012, performed an evaluation of the fetal behavior in normal and high-risk pregnancy during second and third trimesters. The study group included 61 healthy pregnant women and 135 pregnant women with high-risk pregnancy between 24 and 38 weeks of gestation. In all of them KANET was applied, and the scores have significant differences on the two groups of pregnant women. Most fetuses who obtained normal KANET score were found in normal pregnancies, those who obtained borderline score were fetuses with IUGR with increased resistance index (RI) of middle cerebral artery (MCA) and the most fetuses with abnormal KANET score came from pregnancies complicated by threatened preterm delivery with PPROM. The conclusion was that dynamic evaluation of fetal behavior reflects directly the processes of maturation and development of the CNS. This can make the difference between normal and abnormal brain development and may be used for early diagnosis of neurological disorders that become manifest in perinatal and postnatal periods.⁶⁸

In 2013, Kurjak et al made an assessment of fetal behavior with KANET, regarding circulatory changes in umbilical and cerebral arteries. There were 596

fetuses in the high-risk group and 273 fetuses in the low-risk group. The authors found significant behavioral differences when fetal brain circulatory changes were present. It was suggested that in cases of uterine-placental insufficiency, fetal behavioral changes would occur prior to the redistribution of circulation in the brain in hypoxic conditions.⁶⁰

Also in 2013, Kurjak et al conducted a study to analyze the behavior of fetal twins, in order to compare KANET twins with single fetuses in the second and third trimesters. Forty-nine patients were analyzed. The KANET results (normal, borderline and abnormal) had no statistical differences between twins and single. However, isolated scores were statistically different, revealing that twins showed less activity and different patterns of behavior when compared to single fetuses. Although this was observed, a large proportion of twins overall motility might be due to intertwin contacts.³⁵

Athanasiadis et al, in 2013, have applied KANET to assess and compare fetal behavior and neurodevelopment (KANET) between 152 pregnant woman, classified as low-risk (n = 78) and high-risk (n = 74) pregnancies in the second and third trimesters. The neurodevelopmental score was statistically significant higher in the low-risk group compared to the high-risk group. The diabetes subgroup score was significantly higher compared to the IUGR and the pre-eclampsia subgroup. They concluded that neurodevelopment fetal assessment by 4D ultrasound appears to be a feasible technique in the evaluation of high-risk pregnancies, but further studies where any association between KANET score and neurological outcome of the childhood are warranted.⁶⁹

In Brazil, a study was conducted in 2014, when Moreira Neto performed KANET in 51 pregnant women: 17 high-risk and 34 low-risk pregnancies. The results showed a statistically significant difference between groups for all parameters in KANET score 2. For KANET score 0, 5 out of 8 parameters were significantly different. Also, all abnormal KANET results came from high-risk pregnancies and none of low-risk pregnancies presented score zero. Although the study sample was small, it was found a potential to detect and discriminate normal fetal behavior from borderline and abnormal in high-risk pregnancies using KANET.¹³

A comparison of KANET in Asian (n = 89) and Caucasian (n = 78) fetuses was made by Hanaoka et al in 2015. The total KANET scores were normal in both populations, but there was a significant difference in KANET scores between Japanese and Croatian fetuses. When individual KANET parameters were separately compared, they found significant differences in four fetal movements (isolated head anteflexion, isolated



Table 1: List of studies that have applied KANET test to different populations

Author	Year	Study	Study design	Study population	Indication	No.
Kurjak et al ⁴⁹	2008	Cohort	Retrospective	High-risk	Multiple	220
Kurjak et al ⁵⁵	2010	Multicenter	Prospective	High-risk	Multiple	288
Miskovic et al ⁵⁶	2010	Cohort	Prospective	High-risk	Multiple	226
Talic et al ⁴⁵	2011	Multicenter	Prospective	High-risk	Multiple	620
Talic et al ⁵⁷	2011	Cohort				
		Multicenter	Prospective	High-risk	Ventriculomegaly	240
Honemeyer et al ⁵⁸	2011	Cohort	Prospective	Unselected	Unselected	100
Lebit et al ⁶⁷	2011	Cohort	Prospective	Unselected	Unselected	144
Abo-Yaqoub et al ⁵⁹	2012	Cohort	Prospective	High-risk	Multiple	80
Vladareanu R ⁶⁸	2012	Cohort	Prospective	High-risk	Multiple	196
Kurjak et al ⁶⁰	2013	Cohort	Prospective	High-risk	Circulatory changes in umbilical and cerebral arteries	596
Kurjak et al ³⁵	2013	Cohort	Prospective	High-risk	Twins	49
Athanasiadis ⁶⁹	2013	Cohort	Prospective	High-risk	Multiple	152
Neto ¹³	2014	Cohort	Prospective	High-risk	Multiple	51
Hanaoka et al ⁶¹	2015	Cohort	Prospective	Asian and Caucasian	Multiple	167

KANET: Kurjak's antenatal neurodevelopmental test; No.: Number of patients

eye blinking, facial alteration or mouth opening, and isolated leg movement). Their results suggest that ethnicity should be considered when evaluating fetal behavior, particularly during the assessment of fetal facial expressions.⁶¹

CONCLUSION

After Osaka's KANET standardization was published, many excellent studies using this method on fetal behavior have been conducted and published from different centers and some conclusions about the use of KANET test in clinical practice could be made (Table 1).^{8,13,15-17,23,26-32,34-40,45,46,57,60}

The first results indicate that neurological signs in prenatal period, assessed by Kanet, correspond with postnatal development, although in most cases there was not a long-term monitoring of those children.

In 2014, a new KANET consensus statement was created in Bucharest, during the 4th International Fetal Neurology Conference, when it concluded that KANET is ready for use in clinical practice for normal and high-risk fetuses. The test has good sensitivity, specificity, positive and negative predictive values as well as inter and intraobserver reliability. Some limitations to the use of KANET on wide clinical basis are cost of the equipment and adequate training of medical professionals to perform the exam. In addition, when results of KANET and postnatal neurological examination are borderline or even abnormal, it is not easy to predict the future of individual psychomotor development.^{47,48,50}

Therefore, the possibility of improving disease outcomes in children with neurological disorders by the

introduction of early intervention was seen,⁵¹⁻⁵³ and the application of KANET can eventually enhance the ability of physicians to define the neurological risk early enough to intervene postnatally, by introducing physiotherapy, for an example.

It is questionable whether KANET is a screening test for a disease or condition. It was developed to discriminate between fetuses that are at neurological risk and those who are not.⁵⁴ If KANET is considered as a screening test for detection of neural development disability in fetal life, it might also be used as a selective and multiple or multiphasic screening tool.⁵⁴

This new fetal behavior study method gives major contribution to understanding more about functions and development of the fetal CNS. We see in KANET great potential for the investigation of intrauterine neurological deficiencies, however, for this to be achieved, more research is needed in order to be able to use KANET as a screening tool.

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