CASE REPORT

Application of KANET in Special Cases: Part I

Panos Antsaklis, Aris Antsaklis, Nicolaos Papantoniou, Asim Kurjak

ABSTRACT

The detection of neurological impairment during fetal life has been a great challenge in perinatal medicine for many years. Evolution of ultrasound technology has allowed a more detailed examination of the fetal nervous system and earlier detection of central nervous system (CNS) abnormalities. However, overdiagnosis of CNS malformations or variations can be quite confusing from time to time, as we cannot always be sure how these may affect the fetus and as a result we cannot always advise adequately the parents of the affected fetuses about the prognosis. Defining normal and abnormal fetal neurological function *in utero* in order to better predict which fetuses are at risk for adverse neurological outcome could assist with the evaluation of the fetal outcome. Four-dimensional (4D) ultrasound has been used for the assessment of normal neurobehavioral development and has identified characteristics of the fetus that could predict neurological developmental dysfunction. Kurjak antenatal neurodevelopmental test (KANET) is a method that has been shown to offer great advantages for the assessment of fetal neurobehavior, and the findings of KANET have been verified in many studies with postnatal assessments. We present a series of cases where KANET could better improve the evaluation of the prognosis that was made based on ultrasound findings.

Keywords: KANET, 4D ultrasound, Fetal neurobehavior.

INTRODUCTION

The study of fetal nervous system has been a great challenge for obstetricians and neonatologists for many years.[1-4] Human brain development is a very structured process that starts very early during *in utero* life and continuous until adult life, and its integrity is reflected through motor function, mental capacity or a person's behavior as a whole. Defects in brain development may arise during any stage of fetal life and during this period human brain is susceptible to a wide variety of genetic, developmental and acquired abnormalities and insults. The human brain is also sensitive to environmental changes that may affect its growth and development. It is well known, for example that the brain of extremely premature neonates does not reach the genetically programmed growth pattern, even when feeding and nurturing conditions mimic as realistic as possible the condition of intrauterine life.[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).[7] The cause and effect relationship of neurological disabilities however is often uncertain. What is more we have not yet developed a method that would predict to what extent different anatomical abnormalities or variations will affect neurologically the fetus or the neonate. 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.[8-10] Indeed, assessment of the integrity of the fetal nervous system is a major task in modern perinatal medicine.[11]

It is well established that fetal behavioral patterns are directly reflecting developmental and maturational processes of fetal central nervous system (CNS).[8-10] 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 not only structural but also functional abnormalities.[12] 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 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.[13-16] 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).[17] 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.[18-20] 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.[21,22] The first results prove that the prenatal neurological findings as estimated by KANET test, are in concordance with their postnatal outcome.[11]

We present a series of cases in which KANET was applied in order to assess whether it could strengthen the prognosis that was made based on ultrasound findings and further predict the neurological outcome of the fetus.

CASE 1: SEVERE VENTRICULOMEGALY

A 37-year-old woman in her first pregnancy was referred to our center at 28 weeks of her pregnancy because of an incidental finding of fetal ventriculomegaly on routine ultrasound examination, a week earlier before her referral. The woman had already undergone a first trimester ultrasound screening for chromosomal abnormalities (nuchal translucency and biochemical markers) at 12 weeks and 2 days of her pregnancy, which showed a low risk for trisomy 21 (1:2,200). She had also opted to have an amniocentesis at 18 weeks which showed a male fetus with normal karyotype (46XY). She missed the detailed second trimester anatomy scan (anomaly scan) and was seen at 27 weeks, when ventriculomegaly was diagnosed on ultrasound examination and the patient was referred to the Department of Fetal and Maternal Medicine of our hospital. On examination a male fetus with growth corresponding to 26 weeks gestational age and normal amniotic fluid volume was identified. Doppler studies showed normal pulsatility indices (PI) in umbilical and middle cerebral arteries. However, severe right ventriculomegaly was diagnosed, while the fetus appeared grossly hydropic with unilateral right clubfoot (Fig. 1A).

KANET test was performed in order to assess the fetal neurobehavior of the fetus. KANET score was abnormal (score = 1) and it remained abnormal when it was repeated the following day (Fig. 1B).

The couple was informed about the poor prognosis of the condition of the fetus. A follow-up appointment for ultrasound examination was arranged in 1 week time. The following week an intrauterine death was confirmed. The results of TORCH screening showed a highly positive IgG and IgM antibodies titer for CMV infection. The fetus was not sent for a postmortem examination as the couple declined it.

Clinical manifestations of CMV infection (mainly CNS and multiple organ involvement) may be so severe as to lead to a high perinatal mortality rate and major neurologic sequelae in most of the surviving neonates.[23,24] Fetuses with
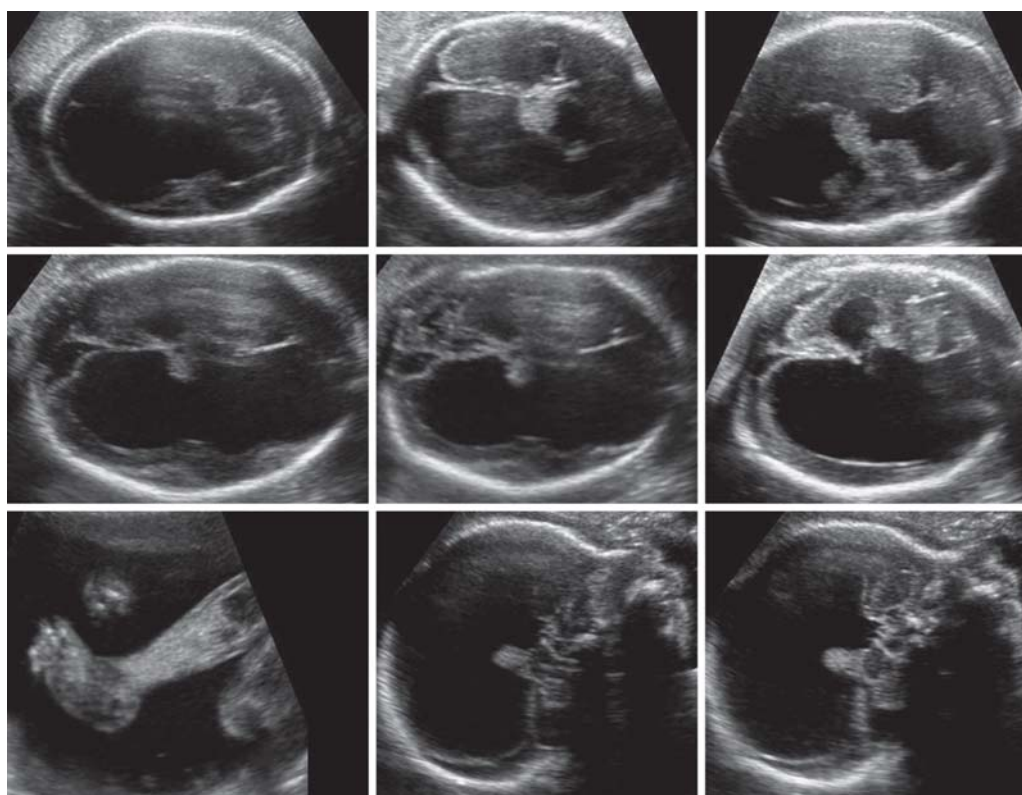

Fig. 1A: Ultrasound findings at 28 weeks of pregnancy. Severe ventriculomegaly mainly of the right lateral ventricle with almost complete replacement of cerebral hemisphere by fluid (hydranencephaly). Abnormal orientation of right fetal foot and ankle (club foot-talipes equinovarus)
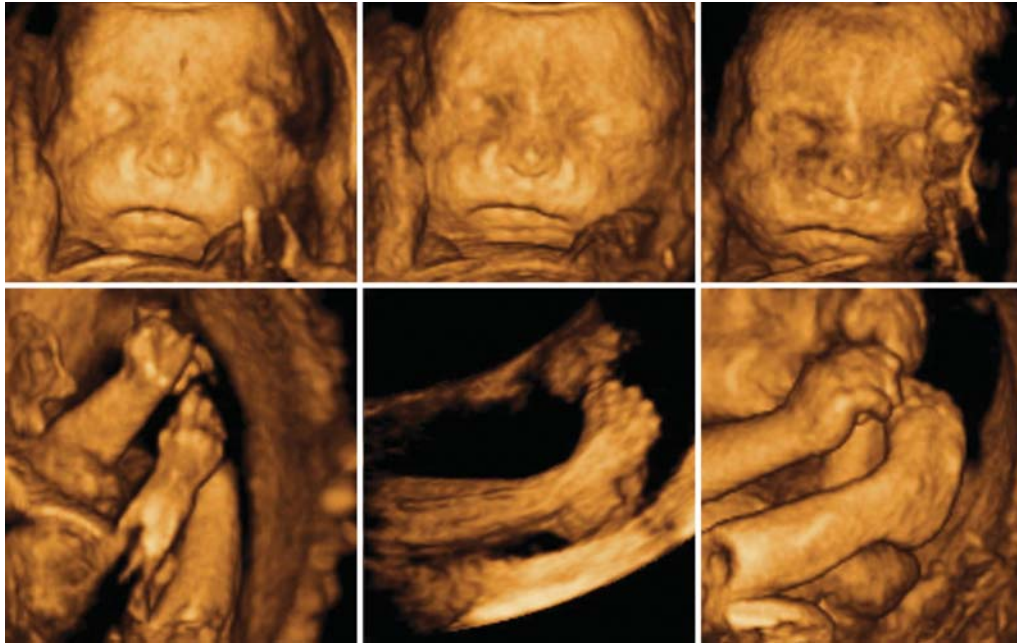
Fig. 1B: The KANET score of the fetus was abnormal (KANET score = 1). No facial alterations or mouth movements were identified on both occasions (frozen face or face-like mask), fists remained clenched during the examinations and no leg movements were seen (right foot deviated inward—club foot)

congenital CMV infection and abnormal ultrasound findings have a high probability of developing postnatal disease.[23,25] When the status of infection is not known in fetuses exposed to maternal CMV infection, ultrasound abnormalities predict symptomatic congenital infection in only a third of cases.[23,26] By contrast, a normal fetal anatomic survey may reassure patients at risk for fetal symptomatic infection, but is associated with a normal outcome in less than half the cases.[23,27] Guerra et al have shown that when fetal infection status is unknown, ultrasound abnormalities predict symptomatic congenital infection in only a third of cases.[23] Addition of fetal neurodevelopmental assessment may further increase the sensitivity of ultrasound examination for the detection of symptomatic infections.

CASE 2: SACROCOCCYGEAL TERATOMA

A 24-year-old woman in her 4th pregnancy was referred to our hospital at 30 weeks of gestation, because of a mass that was identified on routine ultrasound examination. The patient had no previous antenatal visits or ultrasound assessments in the current pregnancy. Ultrasound examination reviled a 13 × 7 cm sacrococcygeal teratoma. The composition of the teratoma was mainly cystic and the color Doppler study showed low vascularity (Fig. 2A).

The fetal growth was at the 15th centile, Doppler studies of umbilical artery and middle cerebral arteries were normal and mild polyhydramnios was noted [amniotic fluid index (AFI) = 22]. No other anatomical abnormalities were detected during the ultrasound examination and no signs of

hydrops fetalis were identified. Patient underwent fetal echocardiography to exclude any other cardiac abnormalities and the development of high output cardiac failure. Follow-up appointments were scheduled every 2 weeks with ultrasound examinations and a consultation with pediatric surgeon was arranged. KANET was performed on every occasion (at 30, 32 and 34 weeks), and the score was every time normal (Fig. 2B).

Special attention was paid on the lower extremities of the fetus, in order to check mobility with 4D ultrasound while performing the KANET (Fig. 2C).

Delivery was performed at 35 weeks of gestation with an emergency cesarean section because of the patient attended the hospital with symptoms of preterm labor. A female neonate weighing 2,350 gm with an Apgar score of 7 was delivered and was transferred to the neonatal intensive care unit (Fig. 2D).

Successful excision of a 12 × 10 × 11 cm mass was performed 3 days after delivery, with a good cosmetic outcome. During the first 6 postnatal months, no postoperative complication and recurrence of tumor have been observed. Functional problems such as feeding, defecation, urination, lower extremity weakness have also not been observed and the current general condition of the neonate is satisfactory.

The prognosis of prenatally detected sacrococcygeal teratoma seems to be related not only to the size of the mass but also to its content.[28] Fetuses with predominantly solid and highly vascularized masses have a poorer prognosis
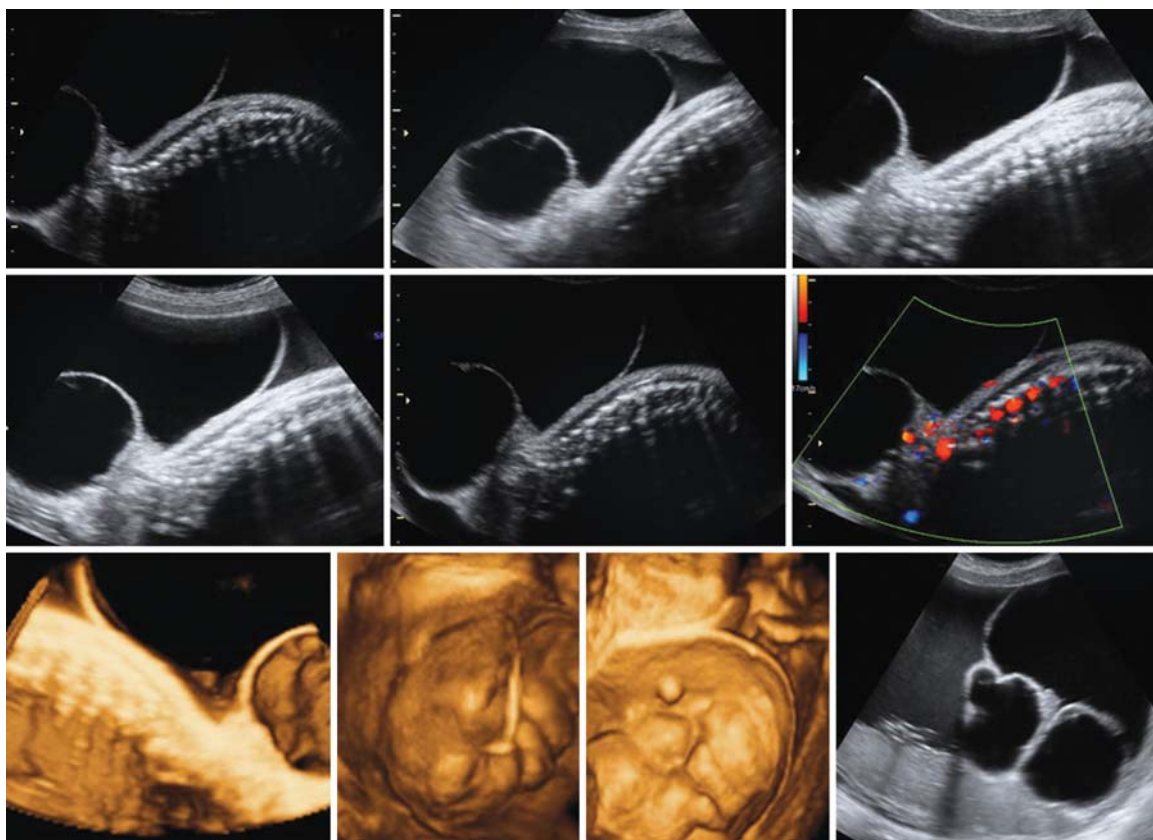
Fig. 2A: Two-dimensional ultrasound images of sacrococcygeal teratoma at 30 weeks of gestation, mainly in sagittal section (sagittal view of the fetal lumbosacral region). Exophytic mixed solid/cystic mass extending from fetal sacrum. Color Doppler shows a small amount of arteriovenosus shunting. The tumor is mainly cystic in structure with low vascularity, which is a good prognostic factor. Also shown three-dimensional ultrasound images of a sacrococcygeal teratoma, in rendering mode, showing the presence of a large mass of lobulated appearance, in which cystic components predominate

Fig. 2B: KANET score was normal. There was fluency of facial alterations (grimace and tongue expulsions) with eye blinking and head anteflexion
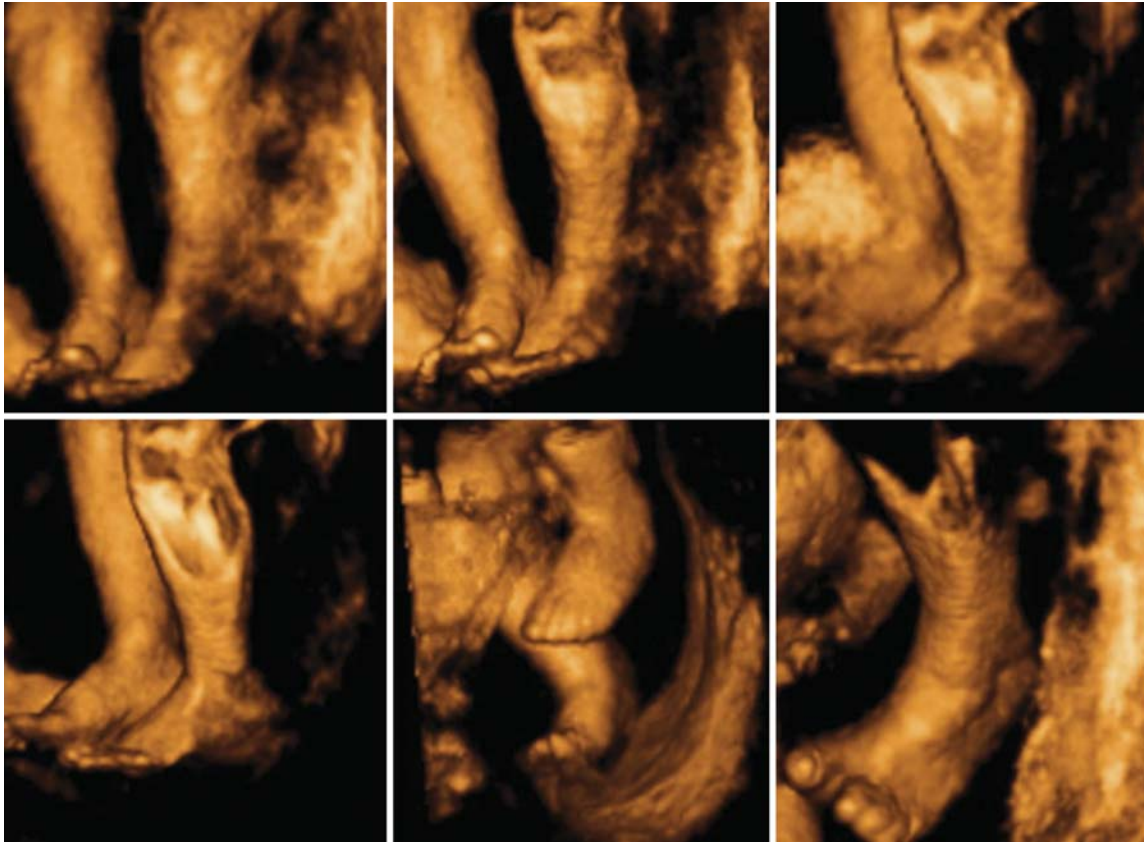
Fig. 2C: Special care was given in the study of the fetal leg movements, using 4D ultrasound as part of KANET score. Leg movements were variable with full range and many alterations giving a good score (n = 2) for KANET

Fig. 2D: Postnatal appearance of sacrococcygeal teratoma prior to resection

than fetuses with tumors that are mainly cystic and avascular in appearance. Fetal sacrococcygeal teratoma has been related to high mortality rate that is related to the secondary effects of the sacrococcygeal teratoma: Prematurity of the infant in cases of preterm labor mainly due to polyhydramnios, dystocia and traumatic delivery especially in undiagnosed cases, exsanguination from hemorrhage into the tumor, or high output failure secondary to a steal phenomenon.[29,30] Wilson et al in a series of 23 cases of

sacrococcygeal teratoma, reported persistent neonatal morbidity that included hip dislocation, sciatic/inferior gluteal nerve palsy, urinary retention, rectal stenosis and severe constipation.[31] We applied KANET to assess neurobehavior of the fetus, that could be affected by the development of high-output cardiac failure and what is more as part of the KANET we paid special attention to the mobility of lower extremities to examine whether we could identify any decrease in the mobility. The positive results

of KANET were confirmed by the postnatal evaluation of the neonate.

CASE 3: HISTORY OF PREVIOUS NEUROLOGICAL PATHOLOGY

A 38-year-old woman in her 2nd pregnancy was scheduled for routine KANET because of previous obstetrical history. With her first pregnancy the patient gave birth at 41 weeks with cesarean section after failed induction of labor for post-term pregnancy. At birth the neonate was apneic, cyanotic and hypotonic and resuscitation was needed. Due to respiratory distress the neonate was intubated and was put under mechanical ventilator support. After birth and until today at 4 years of age, the child still has hypotonia, mainly truncal, muscular weakness, incomplete control of head, absence of tendon reflexes, paresis of the left upper limb, very decreased mobility of right upper and lower limbs, and remains on respiratory support and been fed with nasogastric tube, because of severe swallowing difficulties. Testing for metabolic syndromes, chromosomal and genetic syndromes and neuromuscular diseases came back as negative and MRI examination of the brain showed no pathological findings. The etiology for the condition has not been identified and genetic counseling suggested that probably it was caused by a sporadic event, but a rare inherited condition (e.g. autosomal recessive) could not be ruled out.

In the current pregnancy first trimester scan for screening for chromosomal abnormalities (NT and PAPP-A) showed a low risk for trisomy 21. Amniocentesis at 19 weeks with molecular genetics showed a normal female karyotype (46XX) and detailed anatomy scan at 22 weeks showed no obvious abnormalities. Because of previous history regular KANET assessments were scheduled from 28 weeks on ward (Fig. 3A). Special attention had been paid with 4D ultrasound on the movements of the left arm and fingers, which appeared normal in all examinations (Fig. 3B).

An elective cesarean section was performed at 39 weeks, and a female neonate in very good condition (Apgar 10) was delivered, weighing 3,610 gm. At 10 months of age the neonate is normal and very well in herself, without any neurological or other symptoms.

It is known that the history of a child with neurological pathology increases the risk of recurrence when compared with the general population. For example there is an estimated 5-fold increase in the risk of recurrence in families with a child with CP.[32] The degree of increase and the pathophysiology behind it is not well understood. There are multiple factors, maternal, genetic, environmental and other possible unidentified factors which may in part explain the risk of recurrence of neurological impairment in some occasions. Given that the risk of having a second child with CP is already increased as suggested by different studies, a thorough search for contributing factors is prudent in the

Fig. 3A: KANET at 32 weeks. The KANET had a normal score throughout the pregnancy
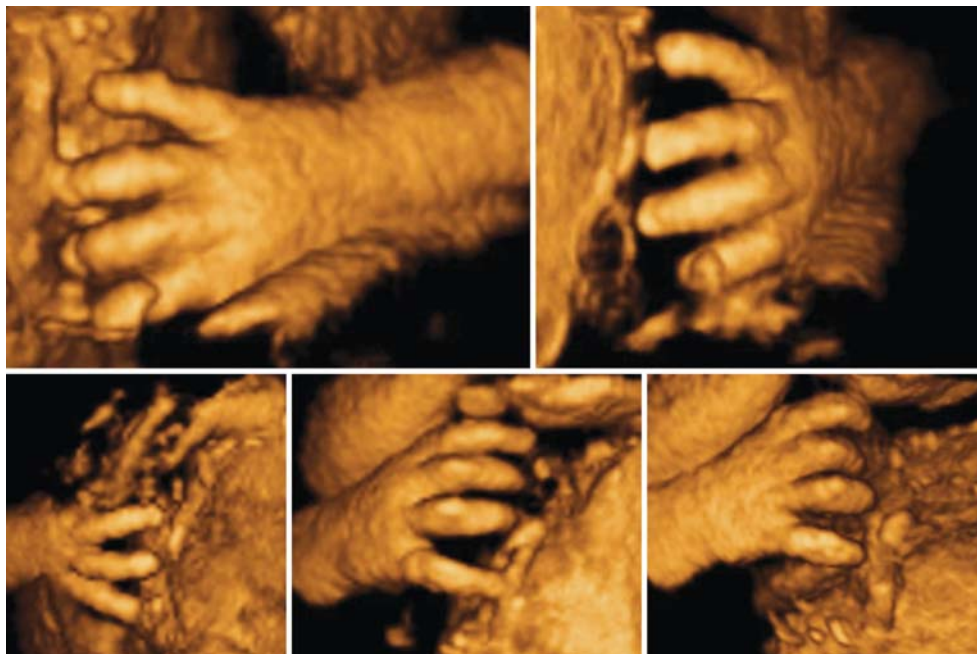
Fig. 3B: KANET was applied every 2 to 3 weeks with normal score every time. Special attention was paid during the KANET to the movements of hands with 4D hands, especially to the left one, due to the previous history

overall assessment of recurrence risk.[33] Studies have shown that fetal behavioral patterns directly reflect developmental and maturational processes of the fetal CNS.[34,35] Fetal behavior can therefore be used as a diagnostic window providing insights into the status of antenatal brain development. 4D assessment of the fetus by using KANET, based on a good understanding of the relationship between fetal behavior and developmental processes in different periods of gestation, may help to differentiate between normal and abnormal brain maturation, enabling the early diagnosis of structural or functional abnormalities, and in some cases reassuring the parents about the positive outcome of the pregnancy.

DISCUSSION

Evolution of ultrasound technologies especially with the development of 3D and 4D methods has made possible the examination of fetal anatomy in explicit detail. As a result, the sensitivity of detecting fetal anomalies with ultrasound examination has increased significantly, and detection of such abnormalities is now achieved earlier in fetal life. These facts allow a more detailed and earlier consultation of the parents, especially of the mother who carries an affected fetus. However, there are times that we may detect an anatomical abnormality or variation, especially of the fetal nervous system, but we cannot predict the prognosis and the consequences of these findings on the postnatal life and who will they affect the behavior of the affected fetus in neonatal life, childhood or adult life. Studies have shown

that there is continuity of behavior from pre- to postnatal life and this relationship is what KANET is attempting to assess.[6,36] KANET test appears to offer a useful predictive tool for better understanding of the state of the fetal neurological function, and how this has been affected by a specific abnormality, giving to the obstetrician an extra method of better counseling the parents, about the prognosis of the condition of their fetus.

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ABOUT THE AUTHORS

Panos Antsaklis (Corresponding Author)

Research Fellow, Department of Obstetrics and Gynecology University of Athens, 11 Lampsakou Str, Athens 11528, Greece Phone: +30-645586417, e-mail: panosant@gmail.com

Aris Antsaklis

Professor and Chairman, Department of Obstetrics and Gynecology, University of Athens, Athens, Greece

Nicolaos Papantoniou

Associate Professor, Department of Obstetrics and Gynecology University of Athens, Athens, Greece

Asim Kurjak

Professor, Department of Obstetrics and Gynecology, Rector of Dubrovnik International University, Dubrovnik, Croatia