Austin Journal of Obstetrics and Gynecology

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Austin Publishing Group

Review Article

Prediction of Future Neurological Abnormalities Based on Fetal Neurobehavior and the Role of Obstetrician in Identifying & Preventing Such Occurrences

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Received: May 07, 2015; **Accepted:** June 08, 2015; **Published:** June 11, 2015

Abstract

Fetal nervous system is especially susceptible to injury during pregnancy and early post-natal period. Injuries to the developing nervous system can later present with a wide range of disabilities, the worst of which are collectively categorized as cerebral palsy. At present the diagnosis of CP and other neurodevelopment abnormalities depend heavily on clinical findings of delayed sensory-motor development, a method that is both unreliable and causes significant delays in diagnosis. Since children with neurodevelopment problems benefit from early efficient intervention, need for novel methods of early diagnosis is evident. One such area of interest involves the assessment of fetal neurobehavioral to predict later neurodevelopment outcomes. KANET is one of the first standardized models developed for this purpose and utilizes 4D ultrasonography for accurate assessment. KANET classifies fetuses as normal, borderline or abnormal depending in neurobehavioral observation. This early identification of fetuses at very high risk of abnormal neurodevelopment, allows the Obstetrician to discuss management option with parents, including termination of pregnancy in severe cases. Parental counseling regarding current and future pregnancies is an important aspect of the process. At present neurobehavioral assessment techniques are in their infancy. Techniques and standards need to be further refined through continued research. The equipment and technologies required remain expensive presenting a barrier to routine implementation of such testing. However the implementation of such techniques may prove to be cost efficient in the long term by helping avoid the significant socio-economic burden and parental trauma caused by cerebral palsy and related disorders.

Abbreviations

KANET: Kurjak Antenatal Neurological test; CP: Cerebral Palsy; CNS: Central Nervous System; GMFCS: Gross Motor Function Classification System; CMV: Cytomegalovirus; LMW: Low Molecular Weight

Introduction

Nervous system is one of the earliest systems that start developing in a fetus. The neural development starts within the 3rd week following fertilization [1,2] meaning that the neural tube, which is of ectodermal origin is one of the first structures to form at a time when most women are unaware of being pregnant. It then differentiates giving rise to various specialized types of neurons and neuro-glial which expand and organize to form the nervous system of the newborn [3], a process that extend all the way into the 3rd trimester of pregnancy [4]. By the time they are born, neonate's brain volume corresponds roughly to a third of the healthy adult brain volume [5] myelination complete by the end of 1st year. Further, brain and the nervous system continue to grow after birth [5,6], especially during the first 3 months of life, growing to a volume just over half of that of a healthy adult at the end of this period [5]. Hence, the developing fetal/ neonatal nervous system is especially susceptible for damage during the antenatal, intrapartum and during the neonatal period. With the advances in pre-natal imaging technologies such as 3D and 4D ultrasonography allowing simultaneous spatial imaging of fetus and its movements, significant efforts have been undertaken to develop systems that use fetal neurobehavioral as a predictor of normal neurodevelopment as well as neurodevelopment abnormalities and future adverse neurological outcomes of the fetus and the neonate. Fetal behavioral patterns have long been considered as indicators of fetal brain development [7,8]. Kurjak Antenatal Neurological test (KANET) was one of the first standardized systems developed for fetal neurobehavioral assessment using 4D ultrasonography [7]. Feasibility of using KANET scoring system for identifying fetuses at risk has been demonstrated in various studies [9 -11] which raises the important possibility that the obstetrician could be the first to observe abnormalities that will predict adverse neurodevelopment outcomes of the neonate. The range of possible adverse neurodevelopment outcomes are often unpredictable, variable and can present as isolated cranial nerve palsy, visual problems, major motor problems (delayed motor- milestones) and sensory and learning difficulties (Sensory and cognitive delays). Profound damage to the nervous system is often manifested as global motor-sensory Cerebral Palsy (CP). It is noteworthy that at present, assessment of CNS damage mostly depends on clinical assessment as opposed to neuroimaging or laboratory studies. One such example is CP where diagnosis

Citation: Dodampahala SH and Meegahawatta AR. Prediction of Future Neurological Abnormalities Based on Fetal Neurobehavior and the Role of Obstetrician in Identifying & Preventing Such Occurrences. Austin J Obstet Gynecol. 2015;2(3): 1042.

is clinical and usually made with the aid of various classification systems. One of the most commonly used classification systems is the Gross Motor Function Classification System (GMFC) [12] which depends on delayed acquisition of motor milestones for diagnosis and classification of CP. However, the diagnoses of CP using such clinical methods remain frustratingly unreliable, especially during the first 18 months of life [13]. For example, in one study, it was found that only 23% of children diagnosed with CP at the age of 7 years had abnormal examinations findings as infants [14]. At the same time it was also found that 50% of the 1 year olds diagnosed with CP became incompatible with the diagnosis by 7 years of age [15]. Early efficient rehabilitation in children with CP has shown to have improved outcomes compared to rehabilitation programs started at a later age. This is likely due to the higher learning ability of the brain in the first 18 months of life. However unreliability in early diagnosis can delay the start of such programs [16]. Therefor the need for a reliable system that can predict the development of CP and other neurodevelopment abnormalities is evident. The development of systems that assess fetal neurobehavior as a predictor of later neurodevelopment abnormalities and adverse neurological outcome offers a possible new approach for such early diagnosis.

The Challenges with Pre-Natal and Post-Natal Assessment of Brain Function

It is debatable to say "are we approaching the era when there will be applicable neurological test for the fetus and assessment of neonate will just be the continuation?". This is still not an easy question to answer because even postnataly there are several methods of neurological evaluation as described above. In utero, where the brain is less mature and the available options for assessment are limited, the process is significantly more complex and many of the methods available today are in their infancy. Past research utilizing functional MRI scanning to detect changes in fetal haemo-dynamic response as well as those that utilize blood oxygen level dependent (BOLD) mapping has clearly demonstrated the ability to detect auditory and visual cortical activation in normal fetuses in the 3rd trimester [17,18].

The Frequency of a Etiological Factors Causing Cerebral Palsy

It is interesting to note that 80% of the cerebral palsies are due to prenatal a etiological factors based on abnormal chromosome, abnormal genetics, abnormal thrombosis, congenital viral and parasitic infection, hypoxia and pre-maturity. Half of the remaining 20% cases are caused due to hypoxic acidotic insults and birth injury during Intrapartum period while the etiology of the remaining 10% remains inconclusive [19]. In most cases, a majority of the insults to the brain remain undetermined, underestimated and unaccounted for. Cerebral palsy, resulting from the most sever insults, in this sense represents the tip of the ice-berg for outcome of such insults, being one the most readily identified neurological problems in children. It is my personal opinion that 90% of the cerebral palsies occur within supervision period of an obstetrician. I also feel that a paediatrician may have to wait until the age of six months postnataly to diagnose a severe CP and nearly 2 months to diagnose a minor cerebral palsy [17, 18].

Frontiers of Antenatal Cerebral Palsy

It is noteworthy, that prevention of chromosomal, genetic and structural abnormalities and aneuploidies involve a careful pre-conception genetic counseling. If recurrent risk or carrier states are identified, avoiding a pregnancy or changing the oocyte or spermatozoa need to be carefully discussed at the preconception stage. A detailed explorative history is mandatory for identifying such risks. In situations where pregnancy is allowed despite a high risk of such disorders, first trimester triple markers, assessment of the nuchal translucency and offering invasive karyotyping needs to be carried out. Termination of pregnancy in the presence of such a disorder confirmed through above investigations invariably reduces antenatal cerebral palsy as well as congenital abnormalities. Other insults that can adversely affect the developing fetal brain include viral infections (e.g. -Rubella, CMV, Parvovirus, Toxoplasma, Listeria Monocytogenes) which can result in viral inclusion body formation and resultant focal cerebral necrosis. Subsequently, necrosis leads to poro-encephalic cysts formation causing viral induced brain damage to the fetus. Fetal cerebral hypoxia and acidosis are also considered to be leading causes for neuronal damage. The damage which is thought to be both structural and functional can be avoided by careful management of pre-natal period. Pre-eclampsia and thrombophilic disorders are two well-known maternal conditions that can lead to fetal hypoxia and acidosis. In pregnancies complicated by such disorders, multidisciplinary management and close fetal surveillance through Doppler studies of the umbilical [20], uterine and duct us venous flow velocities can help reduce complications. Low dose aspirin and LMW heparin are some of the drugs proven to improve outcomes in such pregnancies. Studies indicate that pre-maturity and the low birth weight are the most critical factors for long term neurological mortality in multiple pregnancies [20]. A 1996 study by Pharoah et al found a threefold increase in the rate of cerebral palsy among the twins with birth weight of < 2500 grams, compared to similar weight singletons. He further states that overall, twins suffer double jeopardy due to pre-maturity and low birth weights compare to singletons [21]. The risk becomes greater among the higher order multiple pregnancies. This highlights the need for a degree of caution to be observed by obstetrician during assisted reproductive techniques in sub fertile couples. Emphasis must be put on the transfer of an appropriate number of embryos and selective fetocide in case of multiple order pregnancy above three sacs with the aim of minimizing above complications.

Can we Predict Cerebral Palsy Antenatal?

With some certainty, these are believed to have functional and clinical significance in predicting cerebral palsy antenatal.

- Elevated cytokine levels have been reported in both neonatal blood and amniotic fluid in children with cerebral palsy [22].
- Ultrasound detection of unusual and repeated compression of umbilical cord.
- Tight umbilical cord around the neck
- Observation of specific fetal movements

Altered quality of fetal movements might reveal structural or functional impairment of the fetal system. By definition, fetal behavior

Table 1: First trimester ultrasound features of neurobehavior.

1.	General fetal movements
2.	Startle response
3.	Stretching
4.	Isolated arm and leg movement
5.	Head rotation, ante flexion and retro flexion.

can be defined as any observable action or reaction to an external stimulus by the fetus. These activities can be clearly visualized using the real time 4D volume assessments. They can be spontaneous or elicited by external stimuli. It is believed these behavioral measures provide the best indicators of brain function within the intrauterine life [23]. Development of normal standards of fetal neurobehavioral development is a key requirement to allow comparison of a given fetuses neurobehavior with an aim of predicting neurodevelopment outcome. In one study involving 100 healthy women with normal singleton pregnancies 8 parameters of fetal movement in the first trimester and 14 parameters in the 2nd and 3rd trimesters were assessed longitudinally using 4D ultrasonography between 7 to 40 weeks of gestation. Out of the parameters studied, 7 parameters in the 1st trimester and 11 parameters from the 2nd and 3rd trimesters was found to correlate with the gestational age [24]. The normal movements observed in the first trimester include gross body movements starting between 7 to 8 weeks, limb movements that start around the 10th week and complex movements observed after the 11th week of gestation [23] and are summarized in (Table 1). Normal movements observed in the 2nd and 3rd trimesters include isolated eye blinking, mouthing, yawning, tongue expulsion, grimacing, swallowing, and hand to eye/head/mouth/face/ear movements. Of these, arm movements were found to be the most active in the 2nd trimester while mouth movements were found be least active during the same period. The normal 3rd trimester neurobehavior was found to consist of a rich repertoire movements most of which can be observed postnataly. Thus the 3rd trimester movements are said to possess a high degree of continuity in to the early postnatal period [23]. Normal patterns of neurobehavior observed in 2nd and 3rd trimester are summarized in (Table 2). The visualization of fetal neurobehavior through 4D ultrasound is demonstrated in (Figure 1).

It is also noteworthy that certain movements were seldom noted in normal fetuses but frequently seen in fetuses with abnormal neurobehavior. These include

- hypotonic movements
- high amplitude
- high speed in upper extremities
- emerging abruptly
- burst –pause patterns
- no change in facial expression
- no variabilities in the head movement

Based on KANET assessment the fetuses can be termed, normal, borderline and abnormal following assessment of neurobehavior patterns. KANET assessment is likely to be superior to neonatal neurological assessment and has the added advantage of giving an obstetrician a chance for discussion with the parents about the possible future abnormal neurological outcome and remedial termination of the pregnancy.

Table 2: Second trimester ultrasound features of neurobehavior.

1.	Mouthing
2.	Yawning
3.	Tongue expulsion
4.	Grimacing
5.	Swallowing
6.	Hand to head/face/eye/ear/mouth

Conclusion

Incidence and impact of the problem

It is noteworthy that CP is indeed a great tragedy for an individual, family and society. Globally it affects productivity and wellbeing. And it also poses an immense burden on the society and the economy of the country with its long term cost of maintaining the health of affected individuals. However, the individual trauma to the parents and to the family is usually unaccounted. These parents also regretfully will not give an opportunity for another normal child to be born among them instead focusing all their efforts towards improving the wellbeing of the affected child. Such individual attention focused on affected children by the parents, often damage the chances of successful rearing of other children even when they are present. With these implications in mind, it is important that diagnosis is made as early as possible, with view of counseling, early management or termination. As described above, neurobehavior assessment using 4D ultrasonography has now emerged as a reliable option for early detection of such problems.

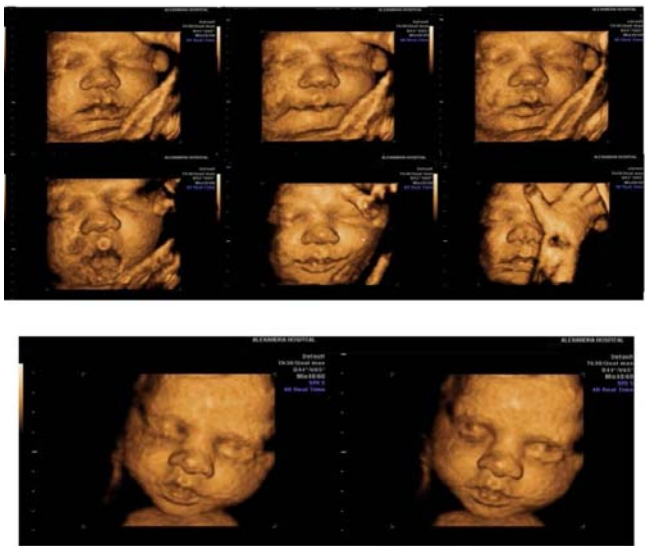

Figure 1: Facial alterations, hand movements and eye blinking during KANET assessment.
Source - Antsaklis.P, Antsaklis.A, Kurjak.A (2013); The Assessment of Fetal Neurobehavior with 4D Ultrasound: the KANET Test; Current Health Sciences Journal; 39 (No 1, January - March) p. 11-19; Available from: http://www.chsjournal.org/archive/vol39-no1-2013/original-papers/the-assessment-of-fetal-neurobehavior-with-4d- ultrasound-the -kanet-test. [Accessed: 1st May 2015].

Technical drawbacks in detecting such problems

However, these investigations and findings are currently limited to specialized units and experimental centers, being still at the very early stages of development. For wider initiation, continued research and practical utilization as well as significant investments in both material and human resources are required.

Recommendation

We strongly recommend that 4D ultrasonography assessment of neurobehavior, for prediction of future neurodevelopment risks be incorporated in to routine Obstetric practice in view of the significant potential improvements in fetal and neonatal outcomes, resulting from early detection of neurodevelopment abnormalities. Due to the significant resources required, we suggest to first start with a selected high risk crowd, attended by staff trained for scanning and counseling etc. The scanning team involved in this process should consist of midwives, nurses, ultra-monographers and counselors, and be led by an Obstetrician. The initial program should target tertiary care centers where most high risk pregnancies are managed, with the long term aim of incorporating the use of neurobehavioral assessment in to the routine assessment process. It is noteworthy if any abnormality is detected in the neurobehavior, these findings should be incorporated in to a well-designed exploring clinical history, detailed anomaly scanning and combined opinion before any termination is recommended. This will prevent unnecessary terminations on isolated finding of an abnormal neurobehavior especially in light of the fact that fetal neurobehavioral assessment is a technology currently in its' infancy based on limited research findings. Author strongly recommend that current practice of identifying abnormal neurobehavior is an important tool in the armamentarium of counseling and prediction of abnormal neural development of the newborn but needs to be used with caution due to lack of a standard scoring system that has been widely verified.

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Austin J Obstet Gynecol - Volume 2 Issue 3 - 2015
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Citation: Dodampahala SH and Meegahawatta AR. Prediction of Future Neurological Abnormalities Based on Fetal Neurobehavior and the Role of Obstetrician in Identifying & Preventing Such Occurrences. **Austin J Obstet Gynecol**. 2015;2(3): 1042.