4D SONOGRAPHY IN THE STUDY OF FETAL CNS FUNCTION

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INTRODUCTION

The development of human brain proceeds through a series of milestones, from induction of the neuro-ectoderm to formation of the neural tube, cephalic folding, proliferation of neurones, migration, synaptogenesis, and wiring. The first steps are probably strictly genetically controlled, but it is difficult to understand how about 30,000 genes involved in the formation of the human brain can control the organization of about 100 billion neurones and their trillions of synapses. One possible solution is multiple combination of gene activity in time and space; another is that genes are just involved in the scaffolding of the brain and only impose certain genetic constraints.[1] Major events in human brain development and peak times of occurrence are described in the Table 1.

Table 1. *Major events in neural development*

Developmental evet	**Peak time of occurrence**
Primar neurulation (dorsal induction)	3-4 weeks
Prosencephalic cleavage (ventral induction)	5-6 weeks
Neuronal proliferation	
Cerebral	2-4 months
Cerebellar	2-10 months postnatal
Neuronal migration	
Cerebral	3-5 months
Cerebellar	4-10 months postnatal
Neuronal differentiation	
Axon outgrowth	3 months-birth
Dendric growth and synapse formation	6 months-1 year postnatal
Synaptic rearrangement	Birth-years postnatal
Myelination	Birth-years postnatal

Neuralation refers to the inductive events that occur on the dorsal aspect of the embryo, the result in the formation of the brain and spinal cord. These events can be divided into those related to the formation of brain and spinal cord exclusive of those segments chordal to the lumbar region, i.e. primary neuralation, and those related to the later formation of the lower sacral segments of the spinal cord, i.e. chordal neural tube formation

or secondary neuralation. Disturbances of the inductive events involved in primary neuralation result in various errors of neural tube closure, which are accompanied by alterations of axial skeleton as well as overlying meningovascular and dermal covering. Disorders of primary neuralation in order of decreasing severity include craniorachischizis, anencephaly, myeloschizis, encephalocele, myelomeningocele, Arnold-Chiari malformation.

Recognised causes include:

(1) Multi factorial inheritance

(2) Single mutant genes (e.g. the autosomal recessively inherited Meckel Syndrome)

(3) Chromosomal abnormalities (e.g. trisomies 13, and 18)

(4) Certain rare syndromes of uncertain modes of transmission

(5) Specific teratogens (e.g. Thalidomide, Valproic acid)

(6) Specific phenotypes of unknown causes.

The second phase of brain development, Prosencephalic development occurs by inductive interactions under the primary influence of the prechordal mesoderm. The peak time period involved is the second and third months of gestation. Development of the Prosencephalon is considered best in terms of three sequential events: Prosencephalic formation, Prosencephalic cleavage and midline Prosencephalic development. Disorders of prosencephalic development are considered best in terms of these three events and the spectrum of pathology varies from a profound dearrangement (e.g. Aprosencephaly) to certain disturbances of midline prosencephalic development and perhaps the most important is sonic hedgehog (Shh).

After the first 6 weeks of gestation, expansion of the cerebral hemispheres occurs by the proliferation of neurons and glia and then by the growth of neural and glial processes. Over the first 3 months of the post-embryogenic period, the full adult complement of neurons proliferate and populate the developing brain. It is a remarkable fact that the neurons formed during this relatively short period may live as long as a century or more. Because differentiated neurons are unable to replicate, they are unable to repopulate the cortex following losses sustained in the perinatal period.

The differentiation of neurons begins after proliferation of neuronal precursors within specific germinal centers that are always in close proximity to the ventricular or pial surfaces of the developing brain. These young neurons, then, must migrate to the site that they will occupy in the mature brain. As neuronal differentiation proceeds, axons are elaborated and grow to specific sites in the brain to establish synaptic contacts with dendrites and somatic neurons. Over the course of months to years, there is a refinement of these synaptic connections, and the axons become ensheathed by myelin.

The awesome complexity of the human brain begins its evolution after the essential external form is established. The events that follow are proliferation of the brain s total complement of neurons, migration of those neuron to specific sites throughout the central nervous system (CNS), the series of organizational events that result in the intricate circuitry characteristic of human brain and finally the ensheathment of thiscircuitry with the neural-specific membrane, myelin. The events span a period from the second month of gestation to adult life.

It is useful to summarize structural development in embryonic and early fetal period, based on many published studies from Croatian Institute for brain research.[1-3] During the embryonic and early fetal period, the histogenetic events (proliferation, migration and early cytoarchitectonic differentiation) lead to the formation of cortical anlage below the pial surface and the formation of different nuclei in the brain stem, diencephalon and basal forebrain.

Events related to the development of neuronal connections (ingrowth of axons, synaptogenesis and development of postysynaptic dendrites) begin during this early fetal period. The earliest afferent axons (of unknown origin) approach the cortical anlage through the marginal and subplate zone. The development of synapses in the human cerebral cortex begins after the formation of the cortical plate at the end of the 8th week of gestation.[2,] This does correspond with the first Doppler detection of cerebral circulation.

In early fetal period very few synapses are found. The number of synapses increases significantly during the formation of the new deep synaptic zone, the so-called subplate zone between 13 and 15 weeks of gestation. Evaluating this early phase of development of the neural connections in the neocortical anlage, one can conclude that connectivity elements (axons, dendrites, synapses) develop in bilaminar fashion, above and below the cortical plate.

Summarizing this period, Kostovic et al emphasize that the major event in early fetal period is the ingrowing of afferent fibers through the special fetal subplate zone. The other important feature is the simultaneous occurrence of intensive proliferation, migration, neuronal differentiation, axonal ingrowth and intracortical synaptogenesis. In contrast to this, earlier developmental periods are dominated by proliferative, migratory processes while later, the perinatal period, is dominated by neuronal differentiation and synaptogenesis. The development of the neuromuscular system and of its functional correlates are now better understood.

This system develops earliest among all components of the nervous system. Indeed, the morphologic, biochemical and physiologic features of the neuromuscular system are among the best understood of neurologic components. Not surprisingly, aberrations of tone, power, and reflexes are among the best described of neurologic phenomena in the human infant.[4]

DEFECTS IN BRAIN DEVELOPMENT

Defects in brain development may arise during all phases of gestation. The timing of the teratogenic event is critical. Insults incurred early in gestation, when the basic structure of the nervous system is being established, tend to have devastating effects on central nervous system structure and function. Later in gestation, the most important developmental events include organizational events in the cortex and myelination of axons. Aberrant development during this period will result in disorders of cerebral cortical function, which in the least affected cases may account for children born with learning disorders or other subtle neurologic dysfunction. In this respect, the events of neural development extend over a protracted period, during which the nervous system may be susceptible to a variety of insults. It is well established that the human brain is susceptible to a wide variety of genetic, developmental and acquired abnormalities and insults. These brain injuries can occur prenatally, perinatally and/or neonatally or postnatally. The spectrum of neurological compromise that may result from such insults extends from behavioral and learning disabilities to severe cerebral palsy.

Besides genetics, the possibility of important environmental influences is suggested by large variation in the incidence as a function of geographical location and, under certain circumstances, social class and season of the year. The interaction of environmental and genetic influences has been demonstrated in experimental studies. Among specific environmental influences, the particularly important

role for vitamin deficiency during the period of neural tube formation is suggested by experimental and recent clinical studies.

The cortical susceptibility to injury also depends on the stages of anatomical maturation of the fetal brain. In the very low birth weight infants, the distinctive white matter lesion, periventricular leukomalacia (PVL) is the major pathological associated of later developmental handicap. Key factors in the pathogenesisof white matter injury include vascular development, the intrinsic vulnerability of the oligodendrocytes to neurotoxic factors, and exposure to maternal/chorionic membrane infection. The maturity of oligodendrocytes precursors is clearly critical, as the period of greatest risk of PVL is before myelination has begun, at time when oligodendrocytes precursors are actively proliferating and differentiating. Such actively differentiating cells have an increased metabolic demand and are sensitive to the excitatory neurotransmitter glutamate and to free radical toxicity because of a developmental lack of anto-oxidant enzymes. Finally, compelling evidence has recently linked prenatal inflammation or infection to fetal/ neonatal brain injury. It is likely that the effect of infection is mediated by systemic inflammation since fetal plasma interleukin levels including interleukins,[1,8,9] TNF-alpha and the interferons, are strongly and independently associated with PVL. Pre-existing metabolic status and chronic hypoxia also modulate the effect of asphyxial insults on fetal brain. For example, neural maturation is markedly altered in intra uterine growth restriction with some aspects delayed and others advanced. This is likely to influence the response to asphyxia but also to introduce a confounding independent affect on neural development. Severe global retardation has been associated with altered neurotransmitter expression, reduced cerebral myelination, altered synaptogenesis and small brain size. There is also good evidence from a range of species that mall, clinically relevant changes in post-ischaemic cerebral temperature can critically modulated encephalopathic processes that are initiated during hypoxia ischaemic insults and which extends into the secondary phase of neuronal loss. Not surprisingly, the role of therapeutic hypothermia in neonatal brain protections currently a hot topic in perinatal medicine.[5]

CEREBRAL PALSY

Indeed, neurological disability is the most feared complication of pregnancy, labor and the neonatal period. The cause and effect relationship, however, is often uncertain. For example, while perinatal asphyxia is certainly capable of causing cerebral palsy are not related to asphyxia. In this sense asphyxial injury to the fetal central nervous system is one of the most vital and yet highly controversial areas of concern in perinatal medicine. For most of the 20th century, the concept of perinatal brain damage centred around cerebral palsy and intrapartum asphyxia. It is only in the last 20 years that this view has been seriously challenged by clinical and epidemiologic studies which have demonstrated that approximately 70–90% or more of cerebral palsy is unrelated to intrapartum events. Most term infants who subsequently developed cerebral palsy are believed to have sustained asphyxial events in mid-gestation. In some cases, prenatal injury may lead to chronically abnormal heart tracings, and impaired ability to adapt to labor which may be confounded with an acute event.[26–32]

Undoubtedly, 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 the fact that two to four children per 1000 newborns are affected by cerebral palsy whose incidence did not change since 1951. Cerebral palsy is a term used to describe a group of chronic condition affecting body movements and muscle coordination. It is caused by damage to one or more specific areas of the brain, usually occurring during fetal development, or during infancy. ''Cerebral'' refers to the brain and ''Palsy'' to a disorder movement or posture. If someone has cerebral palsy that means that because of an injury to their brain they are not able to use some of the muscles in their function in the normal way (palsy). Children with cerebral palsy may not be able to walk, talk, eat or play in the same way as most other children. This type of cerebral damage has an interesting history. In 1862, the orthopedic surgeon Little advanced the hypothesis that the dominant causes of cerebral palsy were prematurity, asphyxia neonatorum, and birth trauma. However, unintended, Little is the father of what has now become a global childbirth litigation industry. Payments to children with cerebral palsy are some of the largest in the select states reach figures beyond $40 million per case.[5]

The research journey, begun years ago, has progressed substantially over the last 25 years. However, despite earlier optimism that cerebral palsy was likely to disappear with the advent of improvements in obstetrical and neonatal care, there has apparently been no consistent decrease in frequency in the past several decades. Isolated pure intrapartum hypoxia accounted for only 4% of moderate to severe newborn encephalopathy. Indeed, intrapartum hypoxia may have been superimposed on preconceptional or antepartum risk factors with preexisting insult in 25% of cases. The causes ofnewborn encephalopathy are heterogeneous and many causal pathways start either preconceptionally or in the antepartum period. Looking specifically at the intrapartum period, it has been observed that there was no evidence of intrapartum hypoxia in over 70% of cases of newborn encephalopathies.

Recently, there have been many advances in a wide variety of scientific areas associated with cerebral palsy. However, it is still not possible to recognize the point at which cerebral damage becomes irreversible in the case of an intermittent type of fetal asphyxia or intrauterine growth restriction. It is possible that the point of irreversible neurological injury could be reached in labor if the fetus has been able to compensate adequately until that time. In recent years increasing emphasis has been placed on prenatal origins of brain injury in the case of neurologically impaired infants. It was found that 25% of infants who died within one neonatal week had prenatal brain damage. Furthermore, a strong evidence was provided that most examples of cerebral palsy were not the result of perinatal asphyxial events in full term infants, but of prenatal intrauterine problems. Therefore, classic causal relationship between birth asphyxia and cerebral palsy should be questioned.

FETAL MOVEMENTS AS POSSIBLE SCREENING PROCEDURE

Some attempts have been made to initiate a prenatal screening system in order to discriminate fetuses from the general population with compromised CNS function. The development of movement patterns has been described as a major maturational process and a sensitive indicator of neurobehavioral organization and future temperamental and cognitive status.[35–41] The real breakthrough in the analysis of fetal movement patterns was due to the introduction of high quality ultrasound equipment which enabled the observer to carry out real-time observations with sufficient dynamics and good image resolution (Figure 1).

The capacity to store observations on video tape for subsequent off-line analysis was a further important factor which greatly facilitated the accuracy of the data. In numerous elegant studies scientists from The Netherlands established most of the fetal behavioral patterns.[6,7,8–12,42]

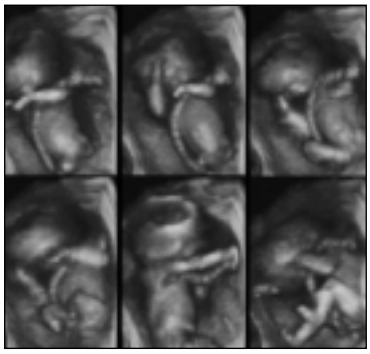

Figure 1. *4D ultrasound sequence of the fetus at 12 weeks of gestation showing general movements. The complex movements of the limb, trunk and head are clearly visible and cause a shift in fetal position. In the first sequence, the right hand is flexed in elbow joint. In the next sequence, the fetus raised the hand and began to deflect in elbow joint. In the last sequence, further elevation of hand is seen*

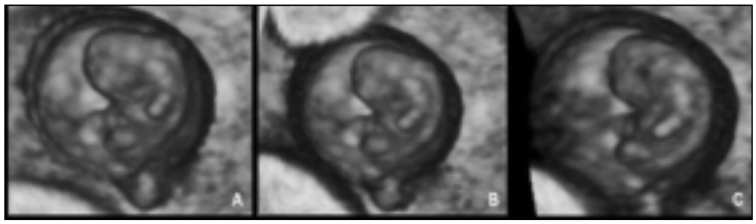

Figure 2. *4D imaging sequence of the fetus at 7 weeks' gestation showing extension of the neck*

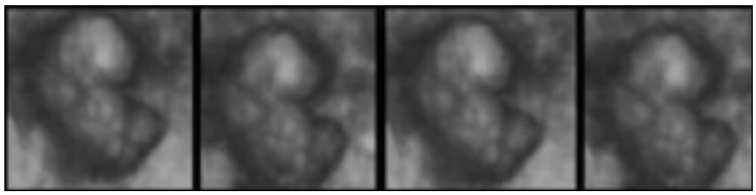

Figure 3. *4D imaging sequence of the fetus at 7-8 weeks' gestation showing a rapid phase contraction of limbs with complex movements involving neck and trunk*

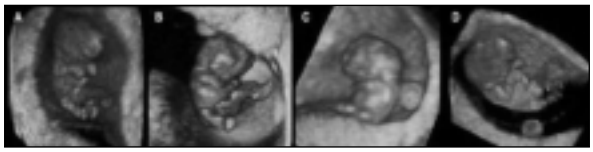

Figure 4. *Fetus at 7-8 weeks of gestation. The fetal hands are located in front of chest and no movements of wrist and fingers are visualized*

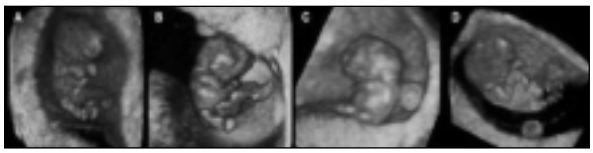

Figure 5. *Fetus at 8-9 weeks of gestation. Isolated hand movements in front of the chest are visualized. Note the wrist and fingers are on the same level*

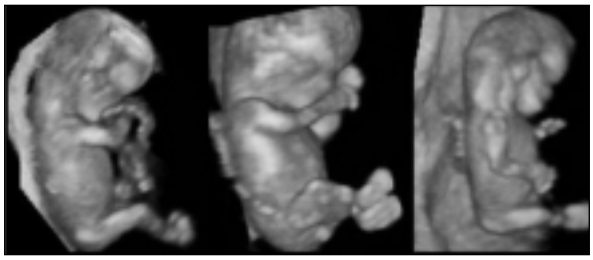

Figure 6. *Fetus at 10-11 weeks of gestation. The fetal hands are moving directly to the face. Note the movements of wrist and fingers are depicted and also lateral rotation of the head is clearly visibled.*

The very first movements seen in any fetus are slow extensions of the neck at 7–7.5 weeks (Figure 2). They are present for a few days and are then followed by the occurrence of startles and general movements. While the first type consists of a rapid phase contraction of all limb muscles, often withsecondary involvement of neck and trunk muscles, the latter are complex movements involving neck, trunk and limbs (Figure 3 and 4). They vary in speed and are forceful but fluctuating in intensity.

After the ninth gestational week the repertoire expands rapidly. Hiccups appear, often in series, for up to several minutes, and isolated arm and leg movements can be observed (Figure 5). This is remarkable in two respects. First, that the young fetus is able to perform isolated movements of one limb at an age when one would expect a longer period of diffuse and generalized motor activity. The second is the unexpected finding of the simultaneous onset of arm and leg movements, unexpected because of the long held principle of a cephalocaudal development in spinal motor functions. After ten weeks, head movements of various types can be seen. They consist of lateral rotation of the head and overextension of the neck (Figure 6).

These movements are carried out with moderate speed and occur in isolation. At about the same age, hand-face contact is seen for the first time. Usually, this is an accidental contact of a hand with the face or the mouth. Between 10.5 and 12 weeks the fetus starts to make breathing movements. At 11 weeks

three new patterns, namely the opening of the jaw, bending forward of the head and complex stretch movements, are added to the repertoire (Figure 7). Somewhat later than the irregular jaw movements, yawns occur. These have the same pattern as in children and adults and hence are easily recognizable. The same holds true for the most complex stretches, which also retain an identical movement form into adult life. At 13 weeks, rhythmical sucking movements, often followed by swallowing, occur in bursts. The rate of these sucking movements at 14 weeks is already about the same as in term infants during breastfeeding. Fetal drinking regulates the amount of amniotic fluid (Figure 8).

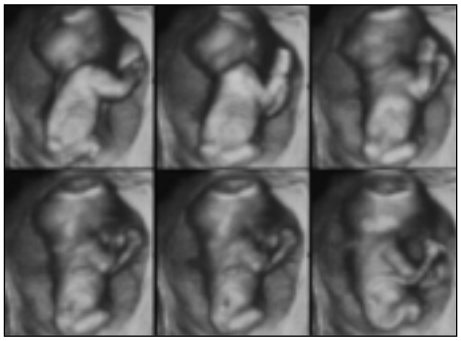

Figure 7. *4D imaging of fetus at 11 weeks demonstrated complex strecth movement involving active arm and hand movements associated with active body and limb movements*

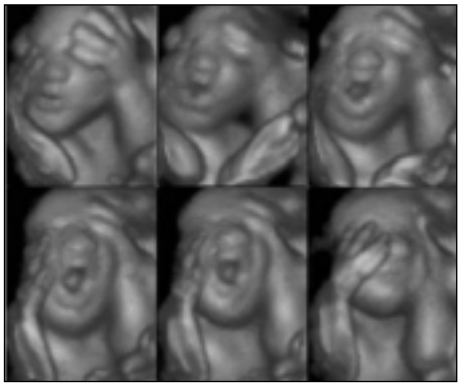

Figure 8. *4D sequence demonstrated fetal drinking and rhythmical sucking movements*

After fetal eye movements (Figure 9) were discovered by Bots et al (1981), Birnholz (1981) reported the onset of slow, rolling eye movements at 16–18 weeks followed by rapid eye movements at 20-22 weeks which include also nystagmoid movements. During the second half of pregnancy hardly any new movement patterns emerge.[4] What is especially noteworthy about fetal movements is the fact that right from the beginning they are patterned into recognizable forms. There is no stage of amorphic and random movements. In the light of recent studies of embryonic neuronal tissue culture, the order as well as the endogenous generation of the fetal movements becomeunderstandable. In order to provide sound data on normal development, the temporal course of the various movement patterns has been studied extensively.[6–8,10,12] The frequently occurring patterns have a clear developmental course in that the general movements show an increase in incidence from 8 to 10 weeks, reaching a plateau at about 15% of the recording time. At the end of pregnancy there is a decline from about 32 weeks onwards. Startles were found to be the most frequent pattern at 9 weeks and to show a gradual decline until 36 weeks. The incidence of eye movements increases gradually from 20 to 36 weeks. The distribution of breathing movements is also established. At 10 and 11 weeks the mode of the interval between consecutive breathing movements is between 2 and 3 s. This is an indication that in the beginning the central respiratory pattern generator works autonomously, and only later is it influenced and modulated, leading to more irregular breathing patterns and consequently to a wider scatter of the interval distribution. Isolated arm movements (Figure 10) increase considerably during the first half of pregnancy, while isolated leg movements (Figure 11)

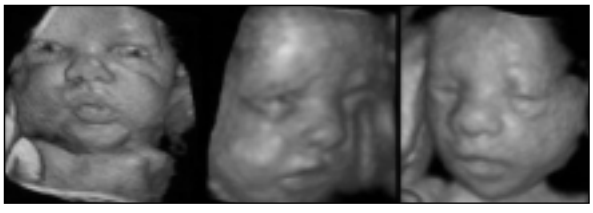

Figure 9. *3D surface rendering demonstrated fetal eyelid opening*

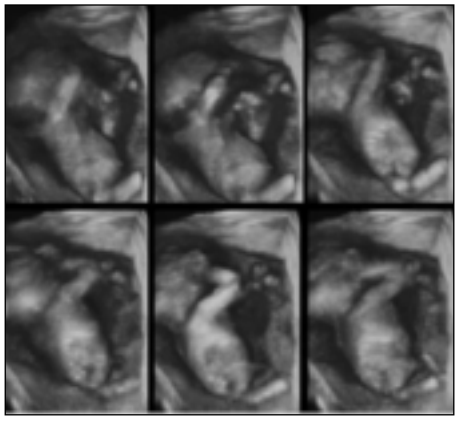

Figure 10. *4D sequence shows isolated arm movement of the fetus at 13 weeks.*

increase up to 15 weeks gestation and decline thereafter until 20 weeks (Table 2). Interestingly, the extensive studies of the quantity of fetal movements and the installation of movement counts as a widely used clinical test failed to detect neurological defects.

Table 2. *Chronology of the functional development of fetal nervous system. Detailed description is given in the text*

Weeks of gestation	Motor system	Sensor system	Circadion rhythm
6	Earliest spontaneous movements gross body movements	Development of taste buds	
		Development of nociceptors	
7		Generalized movements after cutaneous stimulation	
8	Movements of extremities, head trunk, solated limb movements	Localized movements after cutaneous stimulation	
9			
10	Sporadic breathing movements	Penpheral afferents from nociceptors to spinal cord begin to form reflexive renctions to pain	
	Spontatnous movements observed over 15% of 24 hour time	Cutaneous reflexes seen in hands	
11			
12			
13			Spontaneous movements and breathing movements associated with heart rate acceleration
14	Facial movements-swallowing yawing grimacing	Legs sensitive to cuntaneous stimulation-reflexes	
15	Very intensive motor activity 15 different types of body movements can be observed	Secretion of leptin and VP-possible regulation of appetite	
16			
17	Sporadic eye movements		
18		Alterations in cerebra blood flow in response to panful stimul	
19			
20		Nociceptors present all over the body	
21			
22			
23		Elevation of cortisol and beta endorphin levels in response to panful stimuli	
24	Breathing movements observed over 14% of 24 hours period		Consolication of eye movements alternation of eye movements (EM) and non-eye movement (NEM) periods
25		Cochlear function established (22-25 week) Response to vbroacoustic stimulation without lag time	
26			
27			
28			
29			
30	Number of breathing movements charge in response to alteration in CO2 concentration in maternal blood	Fetus responds to purely acoustic stimulation	
31			
32	The number of spontaneous movements begins to decrease		
33			Rapid eye movements (REM) periods and slow eye movements (SEM) periods can be distinguished
34	Breathing movements sensitive to the maternal plasmatic glucose concentration		
35			
36			
37			
38			Constant duration of eye movement and non-eye movement periods integration of eye movements with other parameters of fetal activity heart rate movements)
39			
40			

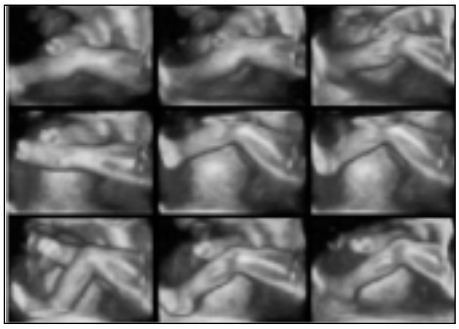

Figure 11. *4D imaging demonstrated isolated leg movements*

What turned out to be different in fetuses, preterm infants and term infants with neural dysfunction is the quality of their general movements. General movements were chosen because of their complex character and their frequent occurrence. Fetuses with prenatally acquired leukomalacia, as documented after birth by cystic abnormalities of their brain which must have occurred at least 10 days earlier, have shown the abnormal pattern of general movements before birth.[12] Unfortunately, there is still no widely accepted diagnostic approach for prenatal detection of cerebral impairment in fetuses with normal growth. In studies on the relationship between fetal motor behavior and the development of the central nervous system, general movements have proved to be of major importance, due to their early emergence, frequent occurrence, and complexity.[43] According to the definition, general movements are motor patterns in which all parts of the body are involved and which may last from a few seconds to a minute. The sequence of arm, leg, neck and trunk movements which follow each other within one general movement is variable. The character of general movements remains essentially unchanged from their emergence until the second month after birth at term. The early emergence of general movements and consistency in pattern provoked research on the clinical significance of fetal movements in the assessment of the integrity of the fetal central nervous system. For this purpose, studies were performed on fetal motor behavior during undisturbed, low risk pregnancies, in which fetal motor behavior was analyzed with respect to the quantity and the quality of the movements. Formerly, the quantity of fetal movements was assessed either by means of maternal counts of perception, or by means of fetal movementrelated frequencies detected by piezo-electric crystals on the maternal abdomen. However, neither method gave direct visual access to the fetus, so that no distinction between the different movement patterns could be made. A significant improvements are expected from the recent introduction of 4D sonography in the accurate and reliable assessment of many behavioral patterns.[13–19]

Four-dimensional sonography is capable of simultaneous spatial imaging of entire fetus and its movements. The fetus can now be simultaneously observed with its movement in three dimensions. Therefore, much more details concerning the quality and direction of movements can be recognized. Using this advantages many fetal activities can be better observed (as illustrated in Figures 1-11). Although clinical research into possible applications of 4D ultrasound is still lacking, the new diagnostic tool seems to be quite promising, particularly for the more accurate and reliable assessment of fetal behavior through all three trimesters of pregnancy. There is potential for possible discovery of neurological test for fetus.

WORK IN PROGRESS

Recently multicentric study of fetal brain function has been established. Some Preliminary reports are already published (ref) and special issue of this Journal included overviews of the all participants.[4,20–24] Interested reader can find there a large number of new information obtained by new technology. The goal of this long term study is to investigate whether the prenatally detected abnormal behavioral pattern increases the number of newly discovered prenatal brain function impairment. We will use 4D US for detailed evaluation of type and quality of fetal movements. Aim of usage of 4D is to find out whether the quality of peripheral and body movements and fetal facial expressions can be used as an additional diagnostic criteria for prenatal brain impairment. Furthermore, other goals are to differentiate prenatal and perinatal brain damage, find out its costs and economic justability, and finally, to evaluate the value of its nation-wide application.

Regarding the fact that fetal brain impairment is a relatively rare condition with incidence 2–4/ 1000 it is necessary to define target population in order to detect the maximum number of cases. In the systematic motor assessment we will study specific movement patterns, quality of speed, amplitude, participating body parts in general movements and quantity in adequate observation period. Additional part of our research will include fetal facial expressions as a possible sign of brain function. In this multiprofessional group of scientists close collaboration between obstetricians, neonatologists, physiologists, child neurologists, genetics and pathologists is established. At this stage of project development high risk population will include patients with family history of neuromuscular-skeletal disorders and prenatally detected structural anomalies like contractures, facial anomalies, subcutaneous edema, abnormal fetal lie and maternal anxiety caused by abnormal fetal movements.

Gravidas from high risk group will be subjected to extensive 3D and 4D ultrasound observation, especially designed to assess whether functional brain impairment had prenatally occurred by the utilization of above mentioned different behavioral patterns.

NEONATAL ASSESSMENT

Current data suggest that 60–70% of neurodevelopmental disabilities are caused during the prenatal period. Efforts to prevent cerebral palsy will require focusing on factors and events during pregnancy. Identification of changes in movement patterns over gestation and postnatally may assist in explicating the role of some of these factors and events.[14,18]

When comparing fetal and neonatal movement patterns, we should always have on mind that fetus is moving in the amniotic fluid, within very precisely defined and bounded environment of stable temperature and composition. The birth process is considered as a major stress or challenge to the infants immature nervous system, and delivery factors play a significant role in shaping infants behavior during the first days of life. Some factors influencing newborns movement patterns are:

- delivery process with the transition to the extra-uterine environment (no water, gravity, unlimited surroundings, visual perception)
- level of the prenatal and postnatal stress
- kangaroo care
- rooming in
- prenatal and postnatal communication with parents
- dietary intake
- light conditions.

The aim of our multicentric research project is to find out whether pathological movement patterns in the fetal period are continuing in the neonatal period and which of them are predictable for the developmental impairment in infants and toddlers. Indeed, numbers of data are supporting the fetal origin of neonatal behavior. It was assumed that individual differences in motor activity level in the first month following birth probably arise during fetal life, and existence of fetal-to-neonatal continuity for numbers of leg movements per minute was proved. Fetal motor activities appear to predict temperament attributes related to regulatory behaviors in early childhood, and they are the basis for individual differences in reactivity and regulation in infancy. Fetal state organization reflects the development of the central nervous system and is a stable individual attribute indicating the postnatal state organization. Fetal movement patterns could reflect the emotional state of the fetus and they might predict how much they are likely to cry postnatally (Figure 12).

Postnatal data collection of term and preterm newborns by video recording of spontaneous movement patterns during the early postnatal period in the hospital are performed according to the Prechtl's methodology.[25] Although the first three days after birth are not recommended for data collection due to physiological instability of the newborns, mentioned period is the best for the assessment of the correlation between the fetal and neonatal movement patterns during active sleep periods. The recorded data of newborn behavioral patterns will then be correlated with in utero 4D recordings regarding the activity level, amplitude and number of movements. At the postnatal age of 6 and 12 months, Bayley Scales of Infant Development II (BSID-II) will be used for the assessment of development. The infants with abnormal development will be rechecked at 18 months. It will be investigated whether developmentally disabled infants had more frequently abnormal fetal and neonatal movement patterns, and whether prenatal motor developmental index (PMDI) could be created to predict neurodevelopmental outcome in infancy and childhood.

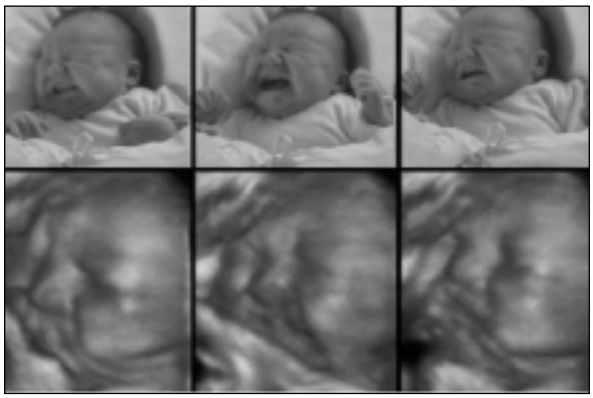

Figure 12. *The emotional state of the fetus prenatally can predict how much they are likely to cry postnatally. Note the fetal facial expression demonstrated in utero using 4D technique is similar to the neonatal period*

CONCLUSIONS

Understanding the structure and function of the fetal nervous system has been the dream of physicians for centuries. The pioneering efforts of Ian Donald in obstetric ultrasound in the latter part of the 20th century have permitted this dream to become a reality. The initial contribution of obstetric ultrasound focused on normal and abnormal structure. Initially, anencephaly was described and followed by increasingly subtle central nervous system abnormalities such as agenesis of the corpus callosum. The current and evolving challenge for investigators in obstetric ultrasound is to have similar success with the understanding of fetal neurological function. There are many functional neurological abnormalities such as cerebral palsy whose causes are poorly understood. This uncertainty regarding causation vitalizes plaintiff's attorneys in the United States and increasingly throughout the world who attempt to relate these neurological abnormalities exclusively to intrapartum eventssuch as usage of oxytocin, forceps deliveries and failure to perform a Cesarean delivery. While there are some cases where causation is probably related to such intrapartum events, this is usually not the case.

Only as our understanding of the precise origin and pathophysiology of neonatal encephalopathy and cerebral palsy advances can logical hypothesis be designed and tested to reduce their occurrence. Indeed, an evolving challenge for the medical profession is to better define normal and abnormal fetal neurological function in utero so that we can better predict antenatally which fetuses are at risk for adverse neurological outcomes irrespective of intrapartum management.[20] Could not the energy and resources invested in our current insurance and litigation system do greater societal good if redirected to scientific research of prevention and direct health care for those affected? The introduction of 4D sonography might help in reaching our goal. However, there is still long way to go.

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