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REVIEW ARTICLE

Continuity from Fetal to Neonatal Behavior: Lessons Learned and Future Challenges

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ABSTRACT

Understanding the relation between fetal and infant behavior and developmental processes of the brain in different periods of gestation may make achievable the distinction between normal and abnormal brain development as well as the early diagnosis of various structural or functional abnormalities. As the development of the brain is unique and continuing process throughout the gestation and after birth, it is expected that there is also continuity of fetal and neonatal behavior, which is the best functional indicator of developmental processes of the brain.

The aim is to present continuity of the general and other movements from prenatal to postnatal life in fetuses and newborns from low- and high-risk pregnancies.

Epidemiological studies revealed that many neurologically impaired infants belong to low-risk population, which means that they seemed to be developmentally normal as fetuses and as infants, while later in childhood neurological disability was diagnosed. Dyskinetic cerebral palsy (CP) is the dominant type of CP found in term-born, appropriate-for-gestational-age children with severe impairments who have frequently experienced adverse perinatal events. As neuroprotective methods of treatment are available for some infants, simple screening methods could be helpful to detect impaired fetuses early enough in order to avoid developmental catastrophe. It has been clear from postnatal assessment of Prechtl's neonatal general movements (GMs) that it is a better predictor of neurodevelopmental disability than neurological examination. Introduction of two-dimensional (2D) and four-dimensional (4D) ultrasound enabled introduction of GMs assessment to the prenatal period. Kurjak et al conducted a study by 4D ultrasound and confirmed earlier findings made by 2D ultrasonography, that there is behavioral pattern continuity from prenatal to postnatal life. New antenatal neurological screening test has been introduced by Kurjak et al (KANET), which was postnatally followed by postnatal neurological screening assessment according to Amiel-Tison (ATNAT). Although many fetal behavioral studies have been conducted in low- and high-risk pregnancies and KANET has been recently standardized, it is still questionable whether the assessment of continuity from fetal to neonatal behavior could improve ability for early detection of brain pathology.

Keywords: Development of central nervous system, Fetal neurobehavior, Four-dimensional ultrasound, General movements, Neonatal neurobehavior.

INTRODUCTION

For centuries, human brain was a black inaccessible box full of mysteries and uncertainties. Physicians were just able to observe outcomes of different pathological processes in the brain sometimes expressed as a neurological disease or disability, while in some psychiatric diseases the brain was anatomically normal, although there was no doubt that the patient was sick. With the development of embryology, physiology, sophisticated imaging, electrophysiological, genetic and other methods, we are becoming aware of some processes taking place in the brain important for the development of every human being.[1] Ultrasound technology and its prenatal and postnatal application in the evaluation of the development of the central nervous system (CNS) can be interpreted only in contrast with the structural developmental events in the particular period of gestation and development.[1] Thus, understanding the relation between fetal and infant behavior and developmental processes in different periods of gestation may make achievable the distinction between normal and abnormal brain development, as well as the early diagnosis of various structural or functional abnormalities.[1-3]

Development of human brain is not completed at the time of delivery and even years afterwards.[1-3] In an infant born at term, characteristic cellular layers can be observed in motor, somatosensory, visual and auditory cortical areas.[1-3] While proliferation and migration are completed in a term infant, synaptogenesis, neuronal differentiation and myelination continue very intensively.[1-3] The developmental processes of the brain are so complex and the possibility for their impairment is very high, which is the reason why congenital malformations of the brain are among the most frequent malformations. Brain is very sensitive to any kind of prenatal or postnatal injury, which may result in developmental disorders.[1] Most of the injuries occur during pregnancy, while intrapartal and postnatal brain injuries are not so frequent.[1] Therefore, it is reasonable to make an effort to diagnose fetuses with brain damage, which is very challenging task prompting the development of fetal neurology. As the development of the brain is unique and

continuing process throughout the gestation and after birth, it is expected that there is also continuity of fetal and neonatal behavior which is the best functional indicator of developmental processes of the brain.[1-3]

The aim of the paper is to present continuity of the general and other movements from prenatal to postnatal life in fetuses and newborns from low- and high-risk pregnancies.

Growth and Brain

The answer to the eternal question concerning the beginning of human life is not simple and unequivocal. It seems that the moment of fecundation is the beginning of new life having the unique potential for development and growth. Prenatal and postnatal potential for growth of the human being is different, with the tendency of slowing down after birth. It seems like potential for growth differs pre- and postnatally, which is still controversial issue.[4] It could be speculated that development of the morphology and the function should be in equilibrium during different developmental stages. It is known that prenatal and postnatal growth potential of the heart, liver, kidneys and lungs is different compared to the brain (Figs 1 and 2).[5]

According to the recent data, it is estimated that mature human brain has 86 billion neurons in total and 85 billion of nonneurons. Cerebral cortex size is 82% of the brain mass with 16 billion neurons which is 19% of total brain neurons.[6] Among primates, humans enjoy the largest number of neurons from which to derive cognition and behavior as a whole.[6] Neocortex, a new and rapidly evolving brain structure in mammals, has a similar layered architecture in species over a wide range of brain sizes. Larger brains require longer fibers to communicate between distant cortical areas; the volume of the white matter that contains long axons increases disproportionally faster than the volume of the gray matter that contains cell bodies, dendrites, and axons for local information processing.[7] Cortical growth is achieved predominantly by an increase in surface area rather than thickness, and during late fetal human development a rapid increase in brain size occurs with considerable development of cortical surface area relative to cerebral volume, manifested in the development of cortical convolutions.[8]

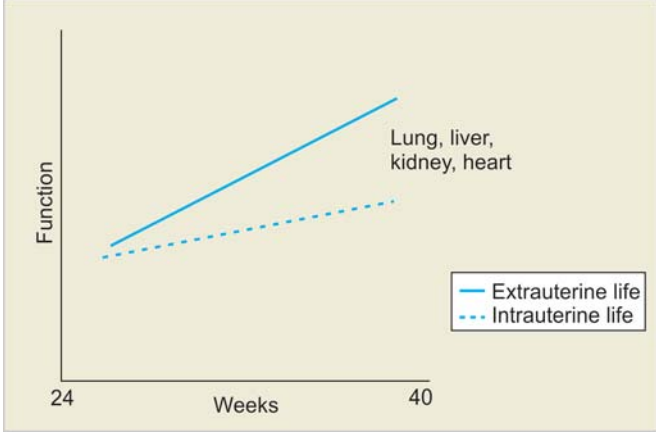


Fig. 1: Potential for prenatal and postnatal growth; potential and function of lungs, liver, kidney and heart[5]

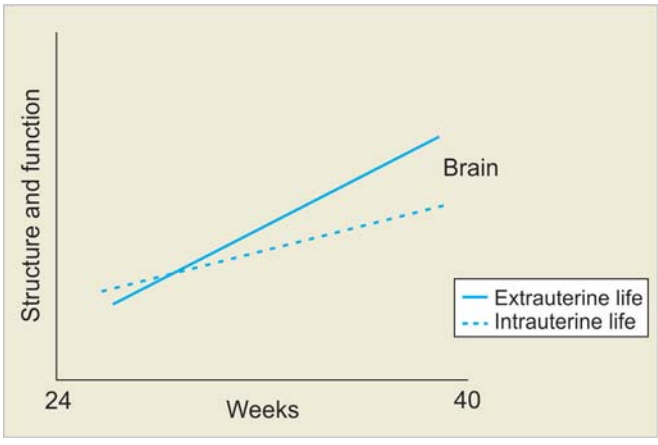


Fig. 2: Potential for prenatal and postnatal brain growth and function[5]

Neurological Disability from Prenatal to Postnatal Life

As it could be learned from fetuses with structurally or functionally abnormal brain, their neurodevelopmental status is disturbed pre- and postnatally.[9] Among other fetuses, we are able to define those who are at neurological risk, among whom we are searching for those who will have developmental disability. Epidemiological studies revealed that many neurologically impaired infants belong to low-risk population, which means that they seemed to be developmentally normal as fetuses and as infants, while later in childhood neurological disability was diagnosed.[10] Dyskinetic cerebral palsy (CP) is the dominant type of CP found in term-born, appropriate-for-gestational-age children with severe impairments who have frequently experienced adverse perinatal events.[10] As neuroprotective methods of treatment are available for some infants, simple screening methods could be helpful to detect impaired fetuses early enough in order to avoid developmental catastrophe.[11,12]

Most infants will be diagnosed as having CP, heterogeneous group of disorders in which sometimes even hereditary elements could be found.[13] Parents of one child with CP had a 4,8-fold risk of having a second affected child, and where the siblings were twins, the risk was 29-fold.[13] These familial risks were particularly high in some clinical subgroups: 17-25 in singletons and 37-155 in twins, including hemiplegia, diplegia and quadriplegia.[13] The remarkably high familial risks are difficult to explain without some contribution of heritable factors.[13]

Even gender is influencing the probability of brain damage in fetuses. If relative maturity of the fetus *in utero* is a form of growth, the short answer to this question might be that male infants are up to a month less mature at term (and presumably also proportionately less mature at earlier gestations) than their female counterparts.[14] This maturity difference is specifically true for cerebral anatomy, lateralization and myelination,[15] and can be measured as differences of *in utero* behavioral adaptation to evoked responses.[14] Such immaturity might make male brains

more vulnerable to insult at a variety of stages including intrapartum stressors. Cerebral palsy (CP) and related developmental disorders are more common in males than in females, but the reasons for this disparity are uncertain.[16] Males born at preterm also appear to be more vulnerable to white matter injury and intraventricular hemorrhage than females. Experimental studies in adult animals and data from adult patients with stroke indicate that sex hormones, such as estrogens provides protection against hypoxic-ischemic injury, and the neonatal brain is also influenced by these hormones. Other reports demonstrated major differences between male and female neurons grown separately in cell culture, suggesting that sex differences in the fetal or neonatal period result from intrinsic differences in cell death pathways.[17] This new information indicates that there are important neurobiological differences between males and females with respect to their response to brain injuries.

Size of the newborn after birth could in some clinical situations be the risk factor for development of CP.[18] Factors associated with aberrant size at birth as the possible risk factors for CP in large and small for gestational age infants are shown in the Table 1.[18]

Analysis of a large European dataset of 4500 children with CP, including both term and preterm births, found that the incidence of CP was 30% higher in males than females.[18] This study also showed that the likelihood of more severe CP was greater at the extremes of birth-weight, with the risk of severe CP increased almost four-fold for male infants with birth-weights at the 97th percentile and 16 times higher for male infants at the 3rd percentile.[18] In another report on the incidence of neurological and developmental disability after extremely preterm birth, the EPICure Study Group found that males had a significantly increased incidence of severe disability, CP and low scores for cognitive functioning at 6 years of age.[19]

CP is the commonest cause of severe childhood disability, the etiology of which is largely unknown.[13] It is an "umbrella" term for disorders of development, movement and posture, resulting in limitations of activity due to nonprogressive impairment of developing brain.[20] The diagnosis of CP is retrospective and it is exceptionally made before the age of 6 months in only most severely affected infants, and the specificity of the diagnosis will improve as the child ages and the nature of the disability evolves.[21] CP does not result from a single event but rather there is a sequence of interdependent adverse events providing to the condition.[22] This time frame of evolving adverse events is something which should be taken into account when considering the possibility of CP diagnosis in infants.[21,22] The understanding of the profile of a child's

Table 1: Risk factors associated with abnormalities of size for gestation in term and near-term infants and their association with risk of CP[18]

Factor associated with aberrant size at birth	*Is it a risk factor for cerebral palsy (CP)?*	*Is risk of CP primarily present in LGA/SGA?*
Congenital anomalies[a]	Yes	No
TORCH infections	Yes	No evidence
Chromosomal defects	Yes	NK
Twinning in the 3rd trimester	Yes	Possibly in very preterm birth (< 32 weeks of gestation)/LGA
Placental[a] and cord anomalies	Yes	No evidence
Pre-ecamptic toxemia[a]	Yes	No
Bacterial genital tract infection	Yes	No evidence
Preterm birth[a]	Yes	No
Maternal starvation	Yes	
Maternal alcohol abuse	Yes	NK
Maternal smoking	NK	
Maternal lung/cyanotic heart disease	NK	
Maternal renal/malabsorption disease	NK	
Maternal diabetes (including gestational)[a]	Yes	NK
Small maternal size or low birth weight	NK	
Socioeconomic deprivation	Yes	No
Neonatal hypothermia	Yes	Little or no contribution
Neonatal hypoglycemia	Yes	Little or no contribution
Intrapartum stress	Yes	No
Clinical signs of birth asphyxia/hypoxia	Yes	No evidence

[a]Indicates a risk factor also associated with large size at birth. Otherwise these are all risk factors for small size.
Abbreviations: TORCH–toxoplasmosis, other infections, rubella, cytomegalovirus, herpes simplex; LGA–large for gestational age; SGA–small for gestational age; CP–cerebral palsy; NK–not known

disability across multiple domains is an ongoing process necessary for appropriate treatment and future planning.[21] This theoretical statement is sometimes very difficult to be practically implemented. An attempt to make early diagnosis of CP should be followed with factors related to pathogenesis, impairment and functional limitations in every patient.[21]

The decreasing trend from the period 1991 to 1994 continued, both in children born at term and especially in those born preterm.[10,21] However, the increase in dyskinetic CP in children born at term was a matter of concern.[21] In this group, a perinatal hypoxic ischemic encephalopathy had been present in 71%. Spastic hemiplegia, diplegia and tetraplegia accounted for 38, 35 and 6% respectively, dyskinetic cerebral palsy for 15%, and ataxia for 6%.[21] There was a further increase in full-term dyskinetic CP.[21] The origin of CP in children born at term was considered to be prenatal in 38%, peri/neonatal in 35% and unclassifiable in 27%, while in children born preterm it was 17, 49 and 33% respectively.[10,21]

Influence of the Gravity on Prenatal and Postnatal Motor Development

Data concerning the influence of the gravity on fetal motor development are contradictory. The concept that the fetus floats in a state of weightlessness cannot be applied to the whole pregnancy, and after the fetus is confined by the uterus, it is exposed to the force of gravity.[23] The fetus is not in significant contact with the walls of the amniotic sac until the very end of pregnancy, and sensory input arising from antigravity activity is absent, which is similar to the conditions of microgravity.[24] It was clearly visible that until 21st week of gestation the fetus is in a condition similar to neutral buoyancy with apparent weight around 5%.[25] After the 26th week the fetus is, to a significant extent, exposed to mechanical stress that occurs due to gravitational forces and has 60 to 80% apparent weight.[25] The development of antigravity muscular control is critical to normal motor development during the first year of life. After birth, the newborn is exposed to the 1G environment. Movement against gravity begins during the first month of life, and by four months of age increased flexion control balances the strong extensor muscle patterns.[26] These movements enable the child to develop weight shifting, which in turn stimulates righting and equilibrium responses.[26,27] The influence of the gravity on prenatal and postnatal development of motility could be considered as discontinuity from prenatal (low gravity) to postnatal life (high gravity), however, it proves that different environmental conditions significantly influence behavior and development. According to this theory, after birth neonate is exposed to the tyranny of gravity up to the age of three to four months, when antigravity forces of the neonate enable to overcome this developmental obstacle.

Neonatal Aspect of Fetal Neurology—Clinical Point of View

Although many powerful imaging and other methods are available to find out the consequences of the brain damage, there is no doubt that clinical methods like the history and clinical assessment are of utmost importance. There are some recently published data concerning hereditary factors involved in the pathogenesis of CP.[13] For parents who had one affected child, the risk of recurrence of CP in another child is considerably increased.[13] In order to identify pathogenesis of the process, neuroimaging methods could be used, among which cranial ultrasound (US), magnetic resonance imaging (MRI), magnetic resonance spectroscopy and diffusion weighted imaging are the most frequently used in very low birth weight premature infants and in term infants with encephalopathy.[21,28,29] Impairment of organs or systems by clinical assessment of muscle tone, strength, and control of voluntary movements for early detection of infants with the risk for CP has been frustrating because 43% of 7-year-old children with CP had a normal newborn neurological examination.[30] Is it possible to change this discouraging fact resulting form our failure to diagnose neurological impairment early enough to intervene? Interests in diagnosis of neurological impairment among ultrasonographers using 4D US have been recently shifted toward prenatal period.[31-34] Most clinicians are aware that in 39.6% of CP cases, no risk factor could be identified, while it was estimated that solely intrapartum risk factors were present in 24.7% of CP cases.[35] The only significant perinatal risk factor was neonatal weight of less than 2500 grams.[35] Are we approaching the era of the development of diagnostic tests to detect nonreassuring fetal status in its intrauterine life to intervene at appropriate time in order to decrease the CP rate?[35] This question seems very futuristic because clinicians have difficulties to detect CP in less than 6-month-old infants.[31] Is there any possibility to improve timing of postnatal diagnosis of neurologically disabled infant? Postnatal assessment is probably easier to perform than prenatal, by using simple and suitable for everyday work screening clinical test with good reliability, specificity and sensitivity.[31] Such tests are still not widely used, while those complicated and time consuming are used mostly for clinical research purposes. There is a possibility for the early and simple neurological assessment of the term and preterm newborns with the aim to detect associated risks and anticipate long-term outcome of the infant, and to establish a possible causative link between pregnancy course and neurodevelopmental outcome.[36] As CP is a disorder of movement and postural control resulting in functional limitations, its diagnosis could be helpful in detection of early impairment.[21] Clinical neurological assessment proposed and practiced by Amiel-Tison is very useful in the early detection of newborns at risk.[36] As already mentioned, development of CNS is very complex and long-lasting process. Therefore, the evaluation of its developmental optimality should be assessed in order to investigate whether the infant is neurologically normal or damaged. Neurological assessment at term by Amiel-Tison (ATNAT) is taking into account neurological maturation exploring so called lower subcortical system developing earlier from the reticular formation, vestibular nuclei and tectum, and upper cortical system developing from the corticospinal

pathways.[36,37] The role of lower system is to maintain posture against gravity while the upper system is responsible for the control of erect posture and for the movements of the extremities.[37] At the corrected age of 40 gestational weeks, optimality assessment consists of head circumference measurement, assessment of cranial sutures, visual pursuit, social interaction, sucking reflex, raise-to-sit and reverse, passive tone in the axis, passive tone in the limbs, fingers and thumbs outside the fist, and autonomic control during assessment.[37] The ATNAT has increasing accuracy in assessing CNS function in the neonate by using simple scoring system, focusing on the most meaningful items, promoting a clinical synthesis at term, for term and preterm infants.[37] It was recognized that clinico-anatomic correlations using high resolution neuroimaging techniques could be helpful in the neurological assessment of newborns, while the neurological examination and the functional assessment of the developing CNS are bringing a new perspective of CNS status in neonatal period.[38] According to the investigation of very low birth weight infants, ATNAT at 40 weeks had a positive predictive value of 33% and negative predictive value of 88% respectively, with similar results for neurodevelopmental assessment at the age of three months.[39] This means that we still need some other methods to be used in order to predict neurodevelopmental outcome of low- and high-risk infants.

Assessment of General Movements (GM)—Crucial Indicator of Development

In the last 30 years, objective assessment of videotaped general movements by Prechtl's method has been shown to be predictive of later CP.[40] The quality of general movements (GMs) at 2 to 4 months post-term (so-called fidgety GM age) has been found to have highest predictive value in the detection of the infants at risk for CP development.[41] It seems that assessment of the quality of GM is a window for early detection of children at high risk for developmental disorders.[41] Method is simple and it is based on so called "gestalt perception", i.e. evaluation of GM complexity, variation and amplitude.[40,41] Assessment of GMs at 2 to 4 months post-term at so-called fidgety GM age has been found to have the highest predictive value for development of CP, if abnormal.[40,41]

Heinz Prechtl's work enabled that spontaneous motility during human development has been brought into focus of interest of many perinatologists prenatally and developmental neourologists postnatally.[40,42] According to the research preceding Prechtl's ingenious idea during the development of the individual, the functional repertoire of the developing neural structure must meet the requirements of the organism and its environment.[40] This concept of ontogenetic adaptation fits excellently to the development of human organism, which is during each developmental stage adapted to the internal and external requirements.[40] It is presumed that the basic rhythmicity and patterning of rhythmic motor patterns are produced by neural networks termed central pattern generators.[43] Fetuses and newborns exhibit a large number of endogenously generated motor patterns, which are presumably produced by central pattern generators located in different parts of the brain.

Prechtl stated that spontaneous motility, as the expression of spontaneous neural activity, is a marker of brain proper or disturbed function.[40,41] The observation of unstimulated fetus or infant which is the result of spontaneous behavior without sensory stimulation is the best method to assess its central nervous system capacity.[40] All endogenously generated movement patterns from unstimulated central nervous system could be observed as early as from the 7 to 8 weeks of postmenstrual age, with developing a repertoire of movements within the next two or three weeks, continuing to be present for 5 to 6 months postnatally.[44] This remarkable fact of the continuity of endogenously generated activity from prenatal to postnatal life is the great opportunity to find out those high-risk fetuses and infants in whom development of neurological impairment is emerging. The most important among those movements are so called general movements (GMs) involving the whole body in a variable sequence of arm, leg, neck and trunk movements, with gradual beginning and the end.[40-42,44] They wax and wane in intensity, force and speed being fluent and elegant with the impression of complexity and variability.[40-42,44] GMs are called fetal or preterm from 28 to 36 to 38 weeks of postmenstrual age, while after that we have at least two types of movements: Writhing present to 46 to 52 weeks of postmenstrual age and fidgety movements present till 54 to 58 weeks of postmenstrual age.[40-42,44] Lack of fluency and existence of considerable variation and complexity are the main characteristics of mildly abnormal GMs.[45] When complexity, variation and fluency are absent, then we are dealing with definitely abnormal GMs.[45]

The quality of each individual movement includes speed, amplitude and force combined in one complex perception.[40-42,44,45] Investigation of normal and neurologically impaired preterm infants showed that except for higher incidence of cloni in the abnormal group, there was no marked difference in the quantity of different motor patterns studied.[46,47] However, video analysis of another group of sick preterm infants revealed a "reduction of elegance and fluency as well as variability, fluctuation in intensity and speed rather than any change in incidence of distinct motor patterns".[46-48] Based on postnatal studies, it would be very important to seek for abnormal quantity and quality of prenatal movements in order to find fetuses neurologically at risk.[48]

Some facts are very important in the assessment of GMs. The first is that evaluation of GMs should be based on the video recorded movements either pre- or postnatally. The second fact is that when assessing GMs one should use so called "gestalt perception", which could be described as overall impression of GMs with standardized procedure.[40] During the perception one should recognize the movement patterns of GMs, then assess their complexity, variability and fluency.[40,41] According to Hadders-Algra, GMs could be classified as normal-optimal,

normal-suboptimal, mildly abnormal and definitely abnormal.[41] This modality of GM assessment is important for the prenatal and postnatal observation of GMs. It is not so important to assess the quantity of GMs, while the assessment of their quality is of utmost importance in terms of the prognosis of neurodevelopmental outcome. They can better predict neurodevelopmental outcome than classical neurologic examination alone.[49]

General Movements in High-Risk Fetuses and Disabled Neonates

GMs were studied in high-risk and disabled neonates with results which are very illustrative for prenatal assessment of GMs in high-risk fetuses. In infants with meningomyelocele between days one and seven, tendon leg reflexes caudal to the meningomyelocele had disappeared in almost all neonates.[50] However, leg movements caudal to the meningomyelocele remained concurrently present with GMs in all neonates after day seven, but their duration decreased when compared with GMs on the day one.[50] In neonates with spina bifida aperta, leg movements caudal to the meningomyelocele concur with GMs, indicating functional neural conduction through the meningomyelocele.[50] The disappearance of these leg movements is caused by lower motor neuron dysfunction at the reflex arc, while neural conduction through the meningomyelocele is still functional.[50]

The same GMs in children with Down syndrome (DS) were characterized by low to low/moderate speed, large to large/moderate amplitude, partially creating impression of fluency, smoothness and complexity, abrupt beginning and end, and few other concurrent gross movements.[51] During the 6 months, all children showed an improvement of qualitative and semi-quantitative evaluation, but it was possible to observe great heterogeneity among children in the evolutionary course.[51] GMs evaluation of children with not known motor problems was normal, showing only slight and transient abnormalities at first month.[51] GMs character of children with DS could be related to central nervous system and peripheral abnormalities characterizing this syndrome.[51] The evaluation of GMs in children with DS could be an early marker of motor impairment and help in early management decisions making.[51]

The incidence of normal GMs in infants with asymmetric intrauterine growth retardation (IUGR) was lower than in their appropriate for gestational age-matched controls.[52] Significant correlations were found between GM quality and neurodevelopmental scores in the IUGR group.[52] The fidgety movements were the most sensitive and specific for prediction of neurologic outcome at the age of two years.[52] The GM assessment can serve as an additional tool for examining the neurologic status of the preterm and term IUGR infants.[52]

Psychomotor delay in children of women with epilepsy was confirmed by traditional neurological examination at 7 days, 4 weeks, 13 weeks and 6 months, while between 9 and 12 months of age, traditional neurologic examination became 'silent'.[53] GM assessment was found to be a better predictor of psychomotor development than neurological examination.[53] Psychomotor delay in the offspring of epileptic women could be diagnosed by GMs and neurologic evaluation, providing complementary information concerning psychomotor development and later outcome of these children.[53]

For predicting motor outcome of very low birth weight (VLBW) infants, the assessment of GM has a positive predictive value of 89% and negative predictive value of 84%; while neurodevelopmental assessment at 40 weeks had a positive predictive value of 33% and negative predictive value of 88% respectively, with similar results for neurodevelopmental assessment at age of three months. GM assessment is a simple, repeatable and nonintrusive technique, and may be a valuable method for the early detection of central nervous system impairment in VLBW infants.[39]

In conclusion, prenatal and postnatal assessment of GMs according to Prechtl's method gives quite new insight on the function and development of central nervous system. This important modality is time consuming and requires some technology and expertise to be practiced, but advantages of its implementation in prenatal and postnatal life are very promising and encouraging in terms of its prognostic value. Postnatal assessment of GMs is well developed and established, while prenatal assessment needs sophisticated real time 4D ultrasonographic or other technology in order to enable more precise assessment of GM quality in fetuses.

Continuity of General Movements from Prenatal to Postnatal Life

It has been clear from postnatal studies of neonatal behavior that the assessment of behavior is a better predictor of neurodevelopmental disability than neurological examination.[48] It is important to mention that postnatal observation of movement patterns was introduced by Prechtl et al in the way that they have been observing spontaneous movements of the infant using video typing and off-line analysis of both the quantity and the quality of the movement.[40,42] They proved that assessment of GMs in high risk newborns has significantly higher predictive value for later neurological development than neurological examination.[40,42,48] Kurjak et al conducted a study by 4D ultrasound and confirmed earlier findings made by 2D ultrasonography that there is behavioral pattern continuity from prenatal to postnatal life.[54] Assessment of neonatal behavior is a better method for early detection of CP than neurological examination alone.[55] It is being speculated that intrauterine detection of encephalopathy would improve the outcome. Although many fetal behavioral studies have been conducted, it is still questionable whether the assessment of continuity from fetal to neonatal behavior could improve ability for early detection of brain pathology. Early detection could possibly rise an opportunity to intervene and even prevent the expected damage.[12] Early intervention programs for preterm infants have a positive influence on cognitive outcomes in the short to medium term.[12]

In our work, we observed that there were no movements observed in the fetuses which were not present in neonates (Fig. 3).[56,57] The most frequent were hand to mouth and hand to face fetal and neonatal movements. Hand to mouth and hand to face movements were more frequent in fetuses than in neonates, while all other hand movements were less frequent in neonates than in fetuses.[56,57]

In our systematic study of fetal behavior by 4D sonography, we were able to observe different expressions and movements of fetal face, but the question is, are they indicating fetal awareness?[58] Is it the facial expression of the fetus that can help in understanding what fetus would like to communicate in utero? As our recent investigation showed, there is a behavioral continuity from fetal to neonatal life, which probably includes facial expression.[56-58] It could be observed on the fetal face whether it is satisfied or unhappy, smiling or worried, self-confident or uncertain, but is it the expression of fetal face the predictor of its normal neurological development?

Figures 4A to 8B shows continuity of some movements from prenatal to postnatal life.

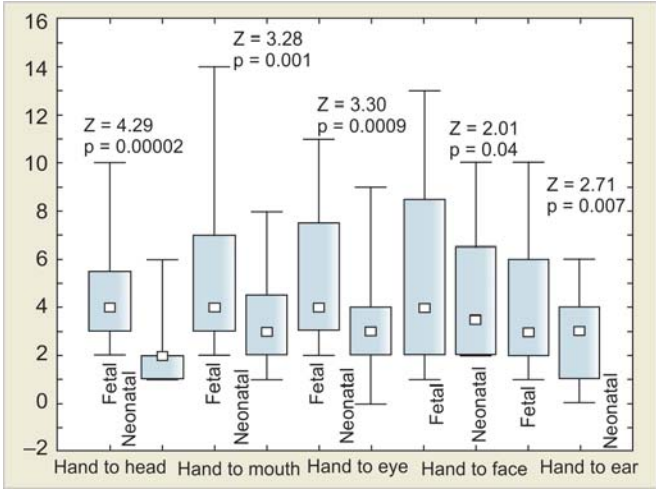


Fig. 3: Comparison of hand movement frequency between fetuses in the third trimester of pregnancy and in neonates[56,57] ‡ Min-Max; □ 25-75%—median value

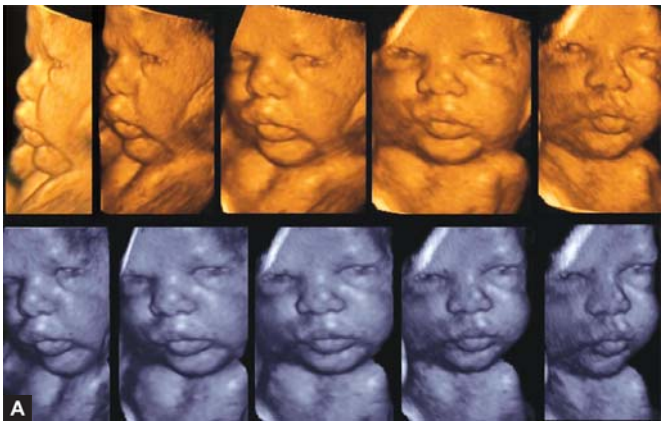
Prenatal Assessment of Some Postnatal Signs of Neurological Disability

It has been proven by now that ultrasonography is a powerful tool in the assessment of fetal behavior. 4D sonography brought up to light visual observation of the fetus, particularly in two especially important domains: Fetal finger movements and facial expressions.[59,60] This new technology is not only a tool of fetal observation but a very useful tool to evaluate the development of fetal CNS in normally developing fetuses and those at high risk. A basic understanding of fetal neurology includes defining of motor pathways involved, chronology of their maturation and direction of myelination.[59,60] This information helps clinician in better interpretation of fetal movements. The experience acquired with the Amiel-Tison's neurological assessment at term (ATNAT) helps in interpretation of fetal movements.[31,36,37,61]

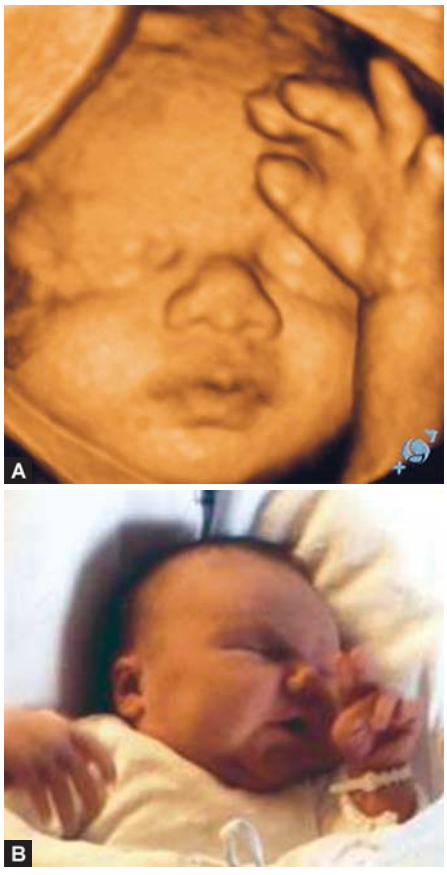
The domain of fetal neurology is already too extensive, but the focus of interest is mainly second trimester, despite the fact that spontaneous fetal mobility emerges and has already became differentiated at a very early age.[62] This means that period of pregnancy from 20 till 40 weeks of gestation, including the end of the neuronal migration and the post-migratory phase corresponding to the development of neocortex will be taken into consideration.[62-65]

As it was already mentioned, CP describes a group of disorders of the development of movement and posture, causing activity limitations, which are attributed to nonprogressive disturbances occurring at the time of fetal brain development.[66-69] Motor disorders, which occur in patients with CP, are often accompanied by disturbances of sensation, cognition, communication, perception, behavior and/or with seizure disorder.[66-69] "Disturbances" is a term referring to events or processes which in some way influence the expected pattern of brain maturation.[61,70] It should be emphasized that morphology does not always correspond to neurological outcome.[31,36,37,61] It would be wise to consider long run prognosis, for each specific type of fetal brain damage and make appropriate decisions for management.[12]

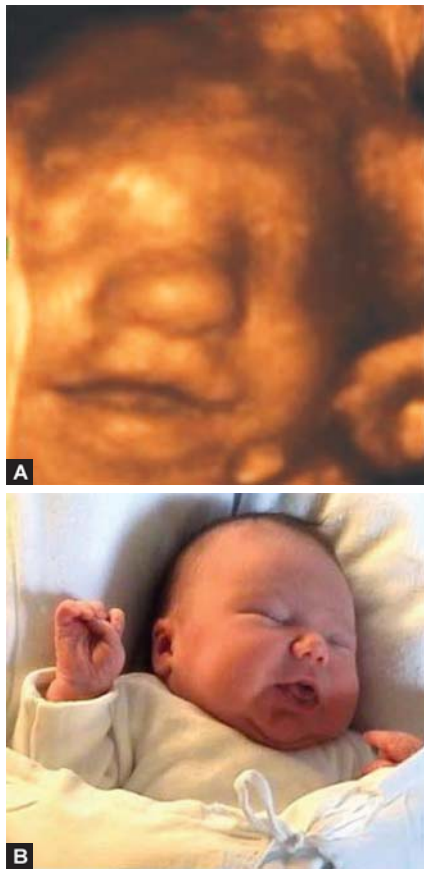
Hopes have been headed towards MRI, but in many cases brain changes can not be detected as early as in the first year of life, e.g. pathological gliosis which causes secondary hypomyelination.[31,36,37,61]



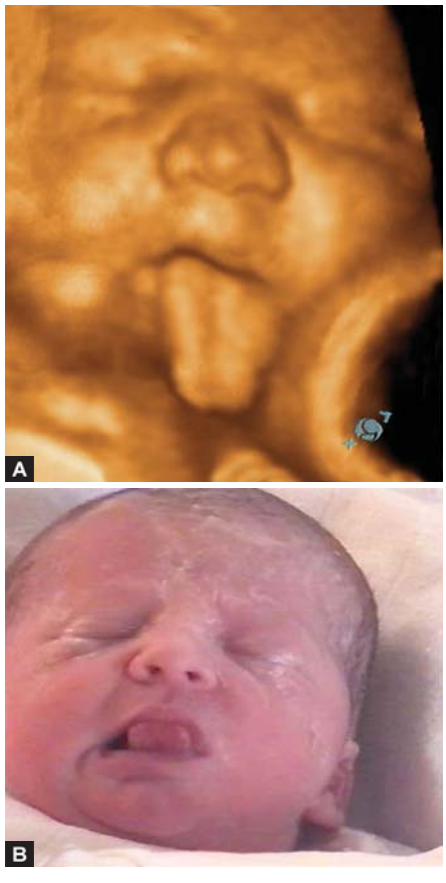
Figs 4A and B: Facial expressions: (A) Fetus (3D ultrasound) and (B) neonate



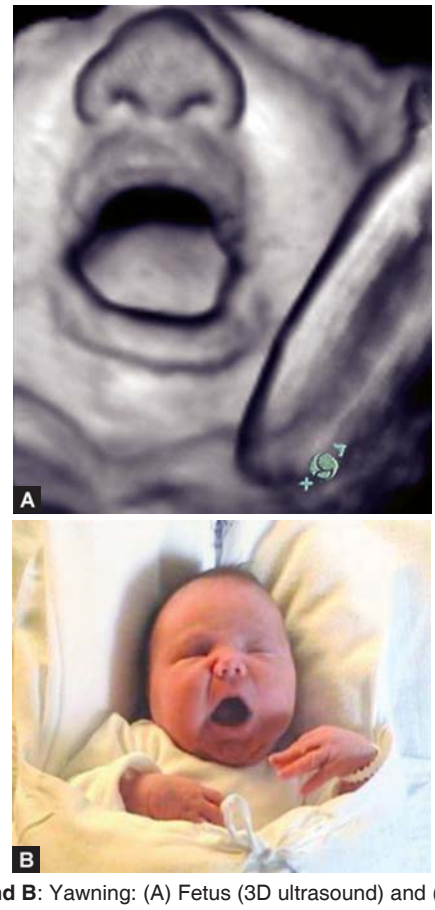
Figs 5A and B: Hand to eye movement: (A) Fetus (3D ultrasound) and (B) neonate



Figs 7A and B: Smiling: (A) Fetus (3D ultrasound) and (B) neonate



Figs 6A and B: Tongue expulsion: (A) Fetus (3D ultrasound) and (B) neonate



Figs 8A and B: Yawning: (A) Fetus (3D ultrasound) and (B) neonate

While examining the fetal head by 4D, sonographer should examine bony structures and fetal cranial sutures, if they are folding over one another, it is considered to be a ominous sign previously described by Amiel-Tison.[31,36,61] The same sign should be searched for postnatally, as a part of neurological examination.[31,36,37,61 70]

The majority of pediatricians believe that the main obstacle for early prediction of CP based on a functional observation of the fetus, such as visual observation by 4D sonography, is due to the "precompetent" stage of most of the motor behavior observed *in utero*.[31,36,37,61,70,71] One of the possible signs detected could be high-arched palate, described by Amiel-Tison, in clinical assessment of the infant nervous system.[31,36,37,61,70] What was believed as prenatally undetectable became visible by 4D ultrasound. Recently, the 3D "reverse face technique" has been described.[55,72] This technique overcomes shadowing of the fetal face by rotating the frontal facial image through 180° along the vertical axis, so that the palate, nasal cavity and orbits become visualized.[53,72]

Pooh and Ogura examined 65 normal fetuses by 3D/4D. The purpose of their study was to investigate the natural course of fetal hand and finger positioning.[73] During the 9th and at the beginning of the 10th week, fetal hands were located in front of the chest and no movements of wrists and fingers were visualized. From the middle of the 10th week, active arm movements were observed.[73] This study is very important, because it is showing that finger and thumb movements begun in the early stage of human life, long before the maturation of the upper system.[70,73] Therefore, this motor activity depends on the lower system and not before 30 to 32 weeks switches to the upper control.[70]

Amiel-Tison also described so-called neurologic thumb squeezed in a fist. Clenched fingers can also be detected by 4D sonography as well as overlapping cerebral sutures.[70]

Head anteflexion becomes visible during 10th and 11th gestational week, according to de Vries et al.[63] However, the activity of flexor muscles will depend on the upper system since 34 weeks of gestation. The absence of active head flexion explored by the raise-to-sit maneuver is one of the major neurological signs at 40 weeks of gestation.[31,36,37,61,70]

Table 2: Inclusion criteria for the study (risk factors)[74]

Family history	Previous child with cerebral palsy
Maternal condition	Diabetes mellitus type I and II, thyroid disease, pre-existent hypertension, drug abuse, thrombophilia, anemia, epilepsy
Pregnancy related disorders	Gestational diabetes, Rh immunization, threatened preterm labor, pre-eclampsia, intrauterine infections, viral illness, cholestasis
Fetal condition	Structural and chromosomal abnormalities, polyhydramnion, intrauterine growth restriction, pathological findings in electrical fetal heart monitoring or Doppler findings

Prenatal to Postnatal Assessment of Infants Born from High-Risk Pregnancies

In the recently published multicenter prospective cohort study, 288 pregnant women meeting the inclusion criteria given in the Table 2 were found eligible to be included in the study of fetal to neonatal behavior from high-risk pregnancies.[74]

The Kurjak antenatal neurological test (KANET) has been used to assess fetal neurobehavior.[75] All neonates underwent postnatal neurological screening assessment according to Amiel-Tison (ATNAT) at the postnatal age of one to three days.[37] After the assessment infants were assigned as normal, borderline or abnormal. Infants from the borderline and abnormal group were assigned to the high-risk group for development of neurological impairment. In this group of infants, for the purpose of this preliminary study, Prechtl's GMs were evaluated at the premature (28 to 36 postmenstrual weeks) and term (37 to 46 postmenstrual weeks) age.[40] After an assessment of GM, infant was classified to one of the groups according to Hadders-Algra: Normal optimal, normal suboptimal, abnormal and definitely abnormal.[41] To simplify the analysis, the infants who were normal optimal and normal suboptimal were considered as 'normal' while the infants who were abnormal were considered as borderline, while those who were definitely abnormal were considered as abnormal. The combined results from the KANET, ATNAT and GM assessment are presented in the Table 3.[75]

Table 3: Combined results from the KANET*, ATNAT** and general movement assessment[75]

Results of postnatal general movements (GMs)		*Postnatal neonatal neurological assessment (ATNAT**)*			*Prenatal assessment (KANET*)*	
		Normal	*Borderline*	*Abnormal*	*Borderline*	*Abnormal*
Normal optimal	4	3	1	0	4	0
Normal suboptimal	20	4	16	0	20	0
Abnormal	6	0	5	1	1	5
Definitely abnormal	2	0	0	2	0	2
Total	32	7	22	3	25	7

* Kurjak antenatal neurological screening test
** Amiel-Tison neurological assessment at term

Abnormal KANET scores have been found in seven fetuses, and 25 fetuses were borderline, which gives all together 32 fetuses at neurological risk. Of seven fetuses with abnormal KANET, postnatal neurological assessment by Amiel-Tison's method (ATNAT) revealed three newborns to be abnormal (arthrogryposis, vermis aplasia and neonate of the mother with the previous child with CP) while four were considered normal (ventriculomegaly, pre-eclampsia, thrombophylia, oligohydramnios).[75] Out of 25 borderline KANET fetuses there were 22 borderline newborns by ATNAT while three were normal (ventriculomegaly, syndrome of intra-amniotic infection, mother's thrombocytopenia).[75] Those who were abnormal prenatally and normal postnatally had following prenatal risk factors: Ventriculomegaly, Dandy-Walker syndrome, skeletal dysplasia, polihydramnios, hydrocephaly, diabetes in pregnancy, nonimmune hydrops, syndrome of intra-amniotic infection, IUGR, trisomy 21, thrombocytopenia, thrombophilia, pre-eclampsia, achondroplasia, oligohydramnios.[75] Out of three abnormal neonates after ATNAT assessment, two had definitely abnormal Prechtl's premature GMs (arthrogryposis and vermis aplasia), and additional six were considered abnormal (neonate of the mother with the previous child with CP, Dandy-Walker syndrome, hydrocephaly, trisomy 21, ventriculomegaly, nonimmune hydrops).[75] Rest of 24 children had normal optimal or normal suboptimal GMs.[75]

In the study of 620 fetuses, from singleton pregnancies KANET scores were studied between 26th and 38th week of gestation.[76] Comparison of KANET scores in 100 low- and 520 high-risk singleton pregnancies were expectedly statistically significant.[76] The largest incidence of fetuses with abnormal KANET was in the group of fetuses who had siblings with CP.[76] The largest incidence of the borderline KANET has been found in the group of fetuses whose mothers had fever during pregnancy.[76] The following parameters of KANET test significantly differed between the fetuses from low- and high-risk pregnancies: Overlapping cranial sutures, head circumference, isolated eye blinking, facial expressions, mouth movements, isolated hand movements, isolated leg movements, hand to face movement, finger movements and general movements.[76]

CONCLUSIONS

Neurological assessment of fetus *in utero* is extremely difficult even after having such sophisticated equipment like 4D ultrasound. As it is well-known that quantity of GMs is not so informative and predictive for neurological impairment, their quality should be assessed. Gestalt perception of premature GMs that we are dealing with *in utero* and several weeks postanatally are not as predictive for the detection of neurologically abnormal fetuses or newborns as fidgety GMs emerging from 54 to 58 weeks of postmenstrual age.[40,41,45] Therefore, some additional parameters should be added to the prenatal neurological examination in order to improve clinicians' ability to make the distinction between normal and abnormal fetuses or to assess optimality of CNS development.[31,36,37,61,70,77] D Pietro states that an emerging consensus recognizes the fact that "fetal neurobehavior reflects the developing nervous system", however, we do not know yet the conceptual and methodological strengths and weaknesses of fetal assessments proposed.[78] We are hardly ready to predict the neurological outcome in fetuses between two extreme situations, optimal or very abnormal. The predictive value for a favorable outcome of a complete neurobehavioral pattern in fetus as from 22 gestational weeks one should be demonstrated. Possibilities of 4D sonography are demonstrating the prenatal onset of a brain damage, based on morphological and functional signs. There is no doubt that this observation will be helpful, even though that prenatally observed signs are not yet highly predictive due to the brain immaturity, their identification will be at least recognized as a retrospective marker for a prenatal insult.[31,36,37,61,70,77]

Are we approaching the era when there will be applicable neurological test for fetus and assessment of neonate will be just the continuation? This is still not easy question to answer, because even postnatally there are several neurological methods of evaluation, while *in utero* we are dealing with more complicated situation and less mature brain. Could neonatal assessment of neurologically impaired fetuses bring some new insights into their prenatal neurological status? It is still unclear and to be investigated. New scoring system for prenatal neurological assessment of the fetus proposed by Kurjak et al (KANET), especially after process of standardization, will give some new possibilities to detect fetuses at high neurological risk, although it is obvious that dynamic and complicated process of functional CNS development is not easy to investigate.[74,75,76,79]

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