REVIEW ARTICLE

Are Fetus and Neonate the Same Individual in Terms of Behavior?

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Abstract

The aim of the paper is to present continuity of behavior from prenatal to postnatal life.

As the development of the brain is a unique and continuing process throughout gestation and after birth, it is expected that there is also the continuity of fetal and neonatal movements, which are the best functional indicator of the developmental processes of the brain. Although we have very powerful imaging and other methods to find out the consequences of brain damage, there is no doubt that clinical methods like history and clinical assessment are of utmost importance. Cranial ultrasound (US) has been used to determine the type and evolution of brain damage. Magnetic resonance imaging (MRI), functional MRI, and near-infrared spectroscopy (NIRS) of the brain have also been used to detect antenatal, perinatal, and neonatal abnormalities and timing of the damage on the basis of standardized assessment of brain maturation. Besides the structure, it is important to investigate the function of the brain, which can be assessed by observation of general movements (GMs). All endogenously generated movement patterns from the unstimulated central nervous system (CNS) could be observed as early as from 7 to 8 weeks of postmenstrual age, with developing a reach repertoire of movements within the next 2 or 3 weeks, continuing to be present for 5–6 months postnatally. Classical postnatal assessment of GMs is well developed and established, while prenatal assessment needs sophisticated real-time four-dimensional ultrasonographic (4D US) or other technology in order to enable a more precise assessment of GMs' quality in fetuses.

It is being speculated that intrauterine detection of neurological disability 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 our ability of early detection of brain pathology. Early detection could possibly raise an opportunity to intervene and even prevent the expected damage. Early intervention programs for preterm infants have a positive influence on cognitive outcomes in short to medium term.

Keywords: Disability evaluation, Fetal movements, Fetal ultrasonography, Neurophysiology.

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Introduction

For more than 20 years, the burden of mental and behavioral disorders in the world has been becoming the main concern in terms of increased healthcare costs and decreased quality of life, without the possibility to intervene early enough to make a substantial change to this tendency.[2,3] Although biological, social, and psychological factors are considered to influence mental and behavioral disorders, it should be pointed out that understanding brain development and function are of substantial significance to better understand the etiology, pathophysiology, epidemiology, prevention, and therapy of those disorders.[2,3] It is well known that most of the disorders affecting the human brain in the perinatal period and infancy are prenatal in origin, making the perinatal period significant for the research of fetal and neonatal behavior.[4]

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Neuroimaging with US technology as the main screening and diagnostic method of brain structure and function, MRI, electroencephalography, magnetoencephalography, and NIRS as diagnostic tools with its prenatal and postnatal application in the evaluation of the development of the CNS can be interpreted only in contrast with the structural developmental events in the particular period of gestation and development.[4–9] Thus, understanding the relationship 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 and/or functional abnormalities of the brain.[10–15]

Development of the human brain is not completed at the time of delivery and even years afterward.[9–16] Most of the injuries occur during pregnancy, while intrapartum and postnatal brain damages are less frequent.[4] Therefore, it is reasonable to make an effort to diagnose fetuses with brain damage, which is a very challenging task prompting the development of fetal neurology. As the development of the brain is a unique and continuing process throughout gestation and after birth, it is expected that there is also the continuity of fetal and neonatal movements, which are the best functional indicator of the developmental processes of the brain.[4]

The aim of the paper is to present continuity of the behavior from prenatal to postnatal life.

Epidemiology and Course of Neurodevelopmental Disability in Perinatal Period

As it could be learned from fetuses with structurally or functionally abnormal brains, their neurodevelopmental status is disturbed pre and postnatally.[5–9] Among other fetuses, we are able to define those who are at neurological risk, among whom we are searching for those who will have a developmental disability.[4] Epidemiological studies revealed that many neurologically impaired infants belong to the 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.[5–7] Higher the neurorisk, higher the incidence of neurodevelopmental disorders. Exposure to only one or two risk factors poses a risk of developing neurodevelopmental disorder in 5% of those exposed while increasing the number of risk factors from 5 to 7% increases the risk of neurodevelopmental disorder to 76 and 99%.[17,18] According to these data, more than half of infants and small children with neurodevelopmental disorders have five or more risk factors, among which the most common were child abuse, mental health disorders, minority status or low education of caregiver, a single parent, poverty, adolescent parent, domestic violence, four or more children in the household, addicted parents, and some others.[17,18] Risk factors can be prenatal, perinatal, and postnatal (neonatal) and are defined differently in different studies.[18,19]

According to the World Health Organization, the prevalence of neurodevelopmental disorders from the age of 2 years in developing countries is up to 10%, while in some regions and countries, it ranges from 2.7 to 15.6%, depending on the study.[2,19,20]

Recent research in developed countries revealed that the prevalence of cerebral palsy (CP) has not changed in the last 60 years, ranging from 1.4 to 2.5 per 1000 live births, despite a six-fold increase in the incidence of cesarean delivery in the same period.[21,22] According to data from Sweden, the prevalence of CP in all gestational ages was 1.96 per 1000 live births, while for each gestational age-group it was as follows: 59.0 per 1000 live births for children born before 28 weeks of gestation, 45.7 per 1000 live births for those between 28 and 31 weeks of gestation, 6.0 per 1000 live births for those between 32 and 36 weeks, and after 36 weeks the prevalence was 1.2 per 1000 live births of that gestational age.[23] One study found a stagnant prevalence of CP in term infants, while it was increasing in preterm infants of all gestational ages, especially those extremely immature, probably due to their better survival.[24] It is thought that the slight increase in CP in the last 25 years is caused by a higher prevalence of CP in preterm rather than term infants.[24] In the aforementioned Swedish study on the incidence of CP according to the clinical picture, hemiplegia was found in 44% of patients, diplegia in 34%, tetraplegia in 5%, the dyskinetic form of CP in 12%, and ataxia in 3%.[24] The following changes were found in the brains of children with CP by neuroimaging methods in the same study: congenital malformations of the brain in 12%, white matter lesions in 49%, cortical-subcortical lesions in 15%, and basal ganglia damage in 11%.[24]

As for the time of onset of damage that caused CP, prenatal causes were found in 38%, perinatal causes in 38%, while there were 24% of unclassified cases.[24] According to data from another study, most of the brain damage (50–75% of them) in children with CP occurs between 24 weeks of postmenstrual age and term age.[25]

Most infants will be diagnosed as having CP, a heterogeneous group of disorders in which sometimes even hereditary elements could be found.[22,26] 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.[22,26] Until recently, 1–2% of CP (mostly familial) had been linked to causative mutations.[4,27] Recent genetic studies of sporadic CP cases using new-generation exome sequencing show that 14% of cases have likely causative single-gene mutations, and up to 31% have clinically relevant copy number variations. In the recently published study of the whole-exome sequencing of 250 parent-offspring trios, it was estimated that 14% of cases could be attributed to an excess of damaging *de novo* or recessive variants, providing evidence for genetically mediated dysregulation of early neuronal connectivity in CP.[27]

Cerebral palsy is the most common cause of severe childhood disability, the etiology of which is largely unknown.[22,28] It is an "umbrella" term for disorders of development, movement, and posture, resulting in limitations of activity due to nonprogressive impairment

of the developing brain.[28] Despite the intention for the early diagnosis of CP lasting for more than two centuries, CP is diagnosed late, between 2 and 5 years retrospectively, exceptionally before the age of 6 months in only the most severely affected infants.[28] CP does not result from a single event, but rather there is a sequence of interdependent adverse events providing to the condition.[28] This time frame of evolving adverse events is something that should be taken into account when considering the possibility of CP diagnosis in infants.[22] The understanding of the profile of a child's disability across multiple domains is an ongoing process necessary for appropriate treatment and future planning.[22] This theoretical statement is sometimes very difficult to be practically implemented. An attempt to make an early diagnosis of CP should be followed with factors related to pathogenesis, impairment, and functional limitations in every patient.[22,28]

Role of Neurological Clinical Assessment in Neonatal Period

Although we have very powerful imaging and other methods to find out the consequences of brain damage, there is no doubt that clinical methods like history and clinical assessment are of utmost importance. There are some recently published data concerning hereditary factors involved in the pathogenesis of CP.[22,28] For parents who had one affected child, the risk of recurrence of CP in another child was considerably increased.[22,28] In order to identify the pathogenesis of the process, neuroimaging methods could be used, among which cranial US, MRI, functional MRI, NIRS, magnetic resonance spectroscopy, and diffusion-weighted imaging are the most frequently used in very-low-birth-weight (VLBW) premature infants and in term infants with encephalopathy.[22,28] 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 for many decades because 43% of 7-year-old children with CP had a normal newborn neurological examination.[29] Even recently, it is estimated that 25–50% of children with neonatal CP will not show signs of suspected CP and will not receive a recommendation for further monitoring of neurodevelopmental outcome.[30] According to a newly published systematic study, it is estimated that neurodevelopmental abnormalities after birth will be found in only one in 500 children who were later suspected of having CP.[31] Is it possible to change this discouraging fact resulting from our failure to diagnose neurological impairment early enough to intervene? Interests in the diagnosis of neurological impairment among ultrasonographers using 4D US have recently shifted toward the prenatal period.[32] 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.[33] The only significant perinatal risk factor was neonatal weight of <2500 gm.[22] Are we approaching the era of the development of diagnostic tests to detect non-reassuring fetal status in its intrauterine life to intervene at appropriate times in order to decrease the CP rate?[28] This question seems very futuristic because clinicians have a lot of difficulties detecting CP in less than 6-month-old infants.[28] Is there any possibility to improve the timing of postnatal diagnosis of neurologically disabled infants? Postnatal assessment is probably easier to perform than prenatal, by using a simple and suitable for everyday work screening clinical test with good reliability, specificity, and sensitivity.[34,35] 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 establish a possible causative link between pregnancy course and neurodevelopmental outcome.[34,35] As CP is a disorder of movement and postural control resulting in functional limitations, its diagnosis could be helpful in the detection of early impairment.[34,35] Clinical neurological assessment proposed and practiced by Amiel-Tison could be very useful in the early detection of newborns at risk.[36] As already mentioned, the development of CNS is a 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 [Amiel-Tison's neurological assessment at term (ATNAT)] is taking into account neurological maturation exploring the 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] The role of the 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 the assessment.[37] The ATNAT is increasing accuracy in assessing CNS function in the neonate by using a simple scoring system, focusing on the most meaningful items and promoting a clinical synthesis at term, for the 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.[36] According to the investigation of VLBW 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 3 months.[36] This means that we still need some other methods to be used in order to predict the neurodevelopmental outcome of low and high-risk infants.

Is Neuroimaging Important for Neonatal Neurological Assessment?

Conventional acquisition neuroimaging techniques, together with modern diffusion tensor neuroimaging techniques, can identify typical patterns of brain injury, even in the early course of the disease.[38–41] However, even though highly suggestive, these patterns cannot be considered pathognomonic. Diffusion tensor neuroimaging techniques can help to distinguish different types of diffuse brain edema.[39,42]

Ultrasound has been a very important diagnostic modality for the detection and follow-up of CNS disorders of sick premature and term babies in neonatal intensive care units for many years.[38,41] It has fairly acceptable sensitivity and specificity in high and low-risk neonatal populations. The validity of the two-dimensional ultrasound (2D US) scans was 85%, sensitivity 70%, specificity 90%, positive predictive value 72%, and negative predictive value 89%, respectively.[43] The 2D US scans classified as low-risk were followed by a normal neurological outcome in 74 (89%) of 83 infants; those classified as high-risk for neurological impairment were followed by abnormal neurological outcome in 21 (72%) of 29 infants.[43] Other neuroimaging procedures like MRI or NIRS are also available and feasible in the neonatal period with better sensitivity and specificity for the detection of hypoxic-ischemic encephalopathy or focal cortical damage, but US remains a very important screening method for the depiction of the fetal and neonatal brain.[40] Neuroimaging is particularly useful to determine the timing of hypoxic-ischemic brain damage.[44] Cranial US has been used to determine the type and evolution of brain damage. MRI, functional MRI, and NIRS of the brain have also been used to detect antenatal, perinatal, and neonatal abnormalities and timing on the basis of standardized assessment of brain maturation.[40] In term and near-term neonates with CP, head MRI revealed focal arterial infarction in 22%, brain malformations in 14%, periventricular white matter abnormalities in 12%, generalized brain atrophy in 7%, hypoxic-ischemic brain injury in 5%, intracranial hemorrhage in 5%, delayed myelination in 2%, other abnormality in 6%, while in 37% of infants' neuroimaging findings were normal.[45]

Although three-dimensional (3D) neurosonography is a safe and low-risk procedure in the neonate, due to very limited availability of equipment for 3D neurosonography, which is often connected with the necessity of newborn transportation, the benefits and risks of 3D imaging should be taken into consideration.[46,47] In the institutions where equipment is available and can be transported to the patient, it is a method of choice for the depiction of the neonatal brain.[47] Indications for 3D in the newborn period are the same as for 2D, and whenever 2D is unreliable or doubtful then 3D is indicated. The main indications for 3D in the newborn period are prenatally or postnatally developed:[46,47]

- Intracranial hemorrhage,
- Hypoxic-ischemic brain damage,
- Inflammatory disorders of the brain and their complications,
- Ventriculomegaly and hydrocephaly (Doppler and volumetric studies included),
- Congenital brain defects, and
- Assessment of gestational age.

Many known and unknown perinatal and social risk factors can influence the development of neonatal brain, especially in premature infants, although abnormal prenatal neurosonography or postnatal neurological findings in apparently well neonates can prompt neonatologists to search for US abnormalities.[48] A correlation was found between US findings in fetal and neonatal period and signs of neurological impairment in the neonatal period and later in childhood in some papers but not in others.[49] Cranial US can be a good predictor of disabling and non-disabling CP at the age of 2 years in low birth weight infants, and it can be in relation to impaired motor function in 5-year-old children.[49,50] Improving the survival of VLBW infants contributed to the increased incidence of CP despite the introduction of sophisticated treatment methods of intensive care.[24] Brain lesions of the white matter diagnosed by US were found to be a powerful predictor of disabling CP.[24] Nevertheless, neuroimaging methods alone are not sufficient to predict the neurological outcome in neonates from high-risk populations.[49] There is a need for more precise clinical and neuroimaging methods applicable in everyday practice in order to improve clinicians' ability to detect neurological handicaps as early as possible and initiate treatment.[49]

Why GMs Count?

Heinz Prechtl's work enabled that spontaneous motility during human development has been brought into the focus of interest of many perinatologists prenatally and developmental neurologists postnatally.[30,51] 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.[30,51] This concept of ontogenetic adaptation fits excellently to the development of human organisms, which is during each developmental stage, adapted to the internal and external requirements.[51] Prechtl stated that spontaneous motility, as the expression of spontaneous neural activity, is a marker of brain proper or disturbed function.[30,51] The observation of unstimulated fetus or infant, which is the result of spontaneous behavior without sensory stimulation, is the best method to assess its CNS capacity.[51] All endogenously generated movement patterns from unstimulated CNS could be observed as early as from the 7 to 8 weeks of postmenstrual age, with developing a reach repertoire of movements within the next 2 or 3 weeks, continuing to be present for 5–6 months postnatally.[52] This

remarkable fact of the continuity of endogenously generated activity from prenatal to postnatal life is a great opportunity to find out those high-risk fetuses and infants in whom the development of neurological impairment is emerging. The most important among those movements are GMs involving the whole body in a variable sequence of arm, leg, neck, and trunk movements, with gradual beginning and end.[52] They wax and wane in intensity, force and speed being fluent and elegant with the impression of complexity and variability.[52] 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 46–52 weeks of postmenstrual age and fidgety movements present till 54–58 weeks of postmenstrual age.[30,51,52] Lack of fluency and the existence of considerable variation and complexity are the main characteristics of mildly abnormal GMs.[30] When complexity, variation, and fluency are absent, then we are dealing with definitely abnormal GMs.[30]

The quality of each individual movement includes speed, amplitude, and force combined in one complex perception.[30,51,52] Investigation of normal and neurologically impaired preterm infants showed that except for a higher incidence of cloni in the abnormal group, there was no marked difference in the quantity of different motor patterns studied.[30,51,52] 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 the incidence of distinct motor patterns."[54] 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.[53]

Some facts are very important in the assessment of GMs. The first is that the 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 the so-called "Gestalt perception," which could be described as an overall impression of GMs with the standardized procedure.[51] During the perception, one should recognize the movement patterns of GMs, and then assess their complexity, variability, and fluency.[30,51] According to Hadders-Algra, GMs could be classified as normal-optimal, normal-suboptimal, mildly abnormal, and definitely abnormal.[30] 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 the neurodevelopmental outcome. They can better predict the neurodevelopmental outcome than classical neurologic examination alone.[54]

In the last 30 years, objective assessment of videotaped GMs by Precht's method has been shown to be predictive of later CP.[51] The quality of GMs at 2–4 months post-term (so-called fidgety GMs age) has been found to have the highest predictive value in the detection of infants at risk for CP development.[51,55] It seems that assessment of the quality of GMs is a window of opportunity for early detection of children at high-risk for developmental disorders.[55] Method is simple and it is based on so-called "Gestalt perception," that is, evaluation of GMs complexity, variation, and amplitude.[30,51,55] Assessment of GMs at 2–4 months post-term at the so-called fidgety GM age has been found to have the highest predictive value for the development of CP, if abnormal.[30,51,55] From that time on, many studies on GMs have been done in high-risk infants, among them meta-analysis of GMs in different age-groups and risks, and comparison with other diagnostic methods.[56–59]

General Movements as a Predictor of Neurologic Disability in the Future—Lesson for Prenatal Assessment

Neurological assessment of preterm infants has not been standardized, and up to now, according to the research, at least 27 assessment measures were identified, and among them, eight fulfilled all clinimetric criteria for neuromotor assessment of preterm infants, which were: suitable for use in preterm infants, discriminative, predictive, or evaluative, designed for serial/longitudinal use, and referenced as a norm.[35] Out of 27 analyzed clinimetric tests for premature infant neurological assessment, the following eight met the study inclusion criteria.[35]

Assessment of Preterm Infants' Behavior (APIB), Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS), Test of Infant Motor Performance (TIMP), Prechtl's Assessment of GMs, Neurobehavioral Assessment of the Preterm Infant (NAPI), Dubowitz Neurological Assessment of the Preterm and Full-term Infant, Neuromotor Behavioral Assessment, and the Brazelton Neonatal Behavioral Assessment Scale.[35] In the absence of a criterion standard for neonatal neuromotor assessments, the NNNS and APIB have strong psychometric qualities with better utility for research,[35] while the Prechtl's Assessment of GMs, TIMP, and NAPI, have strong psychometric qualities but better utility for clinical settings. Prechtl's Assessment of GMs, GMs have the best prediction of future outcomes.[35]

For predicting the motor outcome of VLBW infants, the assessment of GMs 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 the age of 3 months. GMs assessment is a simple, repeatable, and nonintrusive technique, and may be a valuable method for the early detection of CNS impairment in VLBW infants.[60]

A recently published meta-analysis of 47 studies on Prechtl's GMs assessment in the writhing period (till 6 weeks post-term) revealed sensitivity of 93% [with 95% confidence interval (CI) 86–96] and specificity of 59% (95% CI 45–71), respectively, while assessment of GMs in the fidgety period (from 10 to 20 weeks of corrected age) had the sensitivity of 97% (CI 93–99), and specificity of 89% (CI 83–93). Hadders-Algra GMs assessment had a pooled

sensitivity of 89% (CI 66–97) and specificity of 81% (CI 64–91), respectively. Fidgety movements assessed by Prechtl's method reached the strongest predictive validity for later CP, but due to false positive results cannot be considered in isolation.[57] That is why earlier Hadders-Algra in her work proposed that the best prediction of CP can be achieved if complementary neuroimaging and functional techniques are used in longitudinal series.[30]

Assessment of GM is time-consuming, and some investigators put the question of whether this method could be used as a routine assessment of term and preterm infants, and can it replace physical neurological assessment, which is considered not only the observation but also the relevant history taken, thorough examination and relevant plan for the other investigations together with two-way communication of clinician and caregivers.[61] In order to overcome time-consuming obstacles, artificial intelligence (AI) is being used for the assessment of GMs.[62,63] The investigation of AI is based on the transfer the Prechtl's assessment of GMs from visual perception to computer-based analysis using innovative areas of deep learning.[62]

In conclusion, prenatal and postnatal assessment of GMs, according to Prechtl's method, gives quite new insight into the function and development of CNS. This important modality is time-consuming and requires some technology and expertise to be practiced, but the advantages of its implementation in prenatal and postnatal life are very promising and encouraging in terms of its prognostic value. AI use for the assessment of GM is a very promising new field of GMs assessment, which will probably solve the problem of time-consuming assessment for the individual clinician.[62] Classical postnatal assessment of GM is well developed and established, while prenatal assessment needs sophisticated real-time 4D US or other technology in order to enable a more precise assessment of GM quality in fetuses. At the moment, to the best of our knowledge, there is no AI use for the assessment of fetal behavior yet.

Possibility of Longitudinal Assessment of GMs from Prenatal to Postnatal Life

Postnatal studies of neonatal behavior have taught us that the assessment of behavior is a better predictor of neurodevelopmental disability than neurological examination.[54] 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 "offline" analysis of both quantity and quality of the movement.[54] They proved that the assessment of GMs in high-risk newborns has a significantly higher predictive value for later neurological development than neurological examination.[54] Kurjak et al. conducted a study by 4D US and confirmed earlier findings made by 2D US, that there is behavioral pattern continuity from prenatal to postnatal life.[10–15] It is speculated that intrauterine detection of neurological disability 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 our ability of early detection of brain pathology. Early detection could possibly raise an opportunity to intervene and even prevent the expected damage.[63] Early intervention programs for preterm infants have a positive influence on cognitive outcomes in short to medium term.[64]

In our work, we observed that there were no movements observed in the fetuses which were not present in neonates.[10,11] 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.[10,11]

In our systematic study of fetal behavior by 4D sonography, we were able to observe different expressions and movements of the fetal face, but the question was if they were indicating fetal awareness.[65] Is it the facial expression of the fetus that can help in understanding what fetus *in utero* would like to communicate? As our recent investigation showed, there is a behavioral continuity from fetal to neonatal life, which probably includes facial expression.[66] We can see on the fetal face whether it is satisfied or unhappy, smiling or worried, self-confident or uncertain, but is the expression of the fetal face the predictor of its normal neurological development?

Could Some Postnatal Signs of Neurological Disability be Used Prenatally?

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.[5,66,67] This new technology is not only a tool for fetal observation but a very useful tool to evaluate the development of fetal CNS in normally developing fetuses and those at high risk.[68,69] A basic understanding of fetal neurology includes: defining of motor pathways involved, chronology of their maturation, and direction of myelination.[70,71] There have been differences in fetal behavior in male and female fetuses, and psychotropic drugs used by pregnant women may affect fetal behavior as well, which means that these changes should be taken into consideration in fetal and neonatal assessment of behavior.[70,71] This information helps the clinician in better interpretation of fetal movements.[34] The experience acquired with the ATNAT helps in the interpretation of fetal movements.[72]

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.[22–25] Motor disorders which occur in patients with CP are often accompanied by disturbances of sensation, cognition, communication, perception,

behavior, and/or with seizure disorder.[22–25] "Disturbances" is a term referring to events or processes that in some way influence the expected pattern of brain maturation.[22–26] It should be emphasized that morphology does not always correspond to neurological outcomes.[22–26] It would be wise to consider long run prognosis, for each specific type of fetal brain damage and make appropriate decisions for management.[22–26]

While examining the fetal head in 4D, the sonographer should examine bony structures and fetal cranial sutures; if they are folding over one another, it is considered to be an ominous sign previously described by Amiel-Tison.[34] The same sign should be searched for postnatally, as a part of a neurological examination.[72]

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*.[34] One of the possible signs detected could be a high arched palate, described by Amiel-Tison, in the clinical assessment of the infant nervous system.[72] What was believed as prenatally undetectable became visible by the 4D US. Recently, the 3D "reverse face technique" has been described.[73,74] 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.[74] New techniques of image segmentation and computer analysis of 3D US volumes of the fetal face may provide an objective measure to quantify fetal facial features and identify abnormalities.[74] This technique is still not suitable for everyday clinical practice, because the volumes require additional manual segmentation, which is time-consuming.[74]

Pooh and Ogura examined 65 normal fetuses in 3D/4D. The purpose of their study was to investigate the natural course of fetal hand and finger positioning.[75–77] 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.[75] This study is very important because it shows that finger and thumb movements begin in the early stage of human life, long before the maturation of the upper system.[75] Therefore, this motor activity depends on the lower system, and not before 30–32 weeks switch to the upper control.[34]

Amiel-Tison also described the so-called neurologic thumb squeezed in a fist. Clenched fingers can also be detected by 4D sonography, as well as overlapping cerebral sutures.[34,78]

Head anteflexion becomes visible during the 10th and 11th gestational weeks.[34,79] However, the activity of flexor muscles will depend on the upper system from 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.[34]

Influence of the Gravity on Prenatal and Postnatal Motor Development

Data concerning the influence of 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.[80,81] The fetus is exposed to quite a different environment *in utero* than postnatally, which can be explained by the acronym GATO (gravity, age, thermoregulation, and oxygenation), meaning that there is microgravity *in utero* during the fetal period, the age of fetus changes during gestation, and the fetus is exposed to a higher temperature and lower oxygen saturation than the neonate after birth.[81] This hypothesis is called a "baby astronaut" hypothesis which suggests to explain the synergistic effect of these factors on the development of the motor system.[81] 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.[80] It was clearly visible that until the 21st week of gestation, the fetus is in a condition similar to neutral buoyancy with an apparent weight of around 5%.[25] After the 26th week, the fetus is, to a significant extent, exposed to mechanical stress that occurs due to gravitation forces and has 60–80% apparent weight.[81] 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. The movement against gravity begins during the first month of life, and by 4 months of age, increased flexion control balances the strong extensor muscle patterns.[80,81] These movements enable the child to develop weight shifting, which in turn stimulates righting and equilibrium responses.[80,81] The influence of 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, the neonate is exposed to the tyranny of gravity up to the age of 3–4 months when antigravity forces of the neonate enable it to overcome this developmental obstacle.[82]

Significance of Early Intervention and Other Procedures to Improve Neurodevelopmental Outcome in Children with Neurological Risk

Neurodevelopmental disorders could be significant from a social, economic, medical, and individual point of view. Many interventions can have a possibly positive impact on the course of disability depending on the time of onset of damage and its localization and severity. Accompanying comorbidities such as intellectual disabilities, behavioral speech and feeding disorders, epilepsy, sleep disorders, blindness, deafness, incontinence, hip dysplasia, and many others can influence the course and the outcome

of the primary neurodevelopmental disability. In order to improve the neurodevelopmental outcome and reduce the consequences, it is necessary to include affected infants in early intervention programs (habilitation and rehabilitation) as early as possible.[83] It is important to start interventions in the perinatal period that act neuroprotective and can possibly reduce the frequency of neurodevelopmental disorders postnatally.

Interventions in Pregnancy that affect the Incidence of Neurodevelopmental Disorders Postnatally

According to the results of systematic research, it has been proven that some interventions in pregnancy reduce the frequency of neurodevelopmental damage postnatally. According to the above meta-analysis (including 27 controlled randomized trials involving 32,490 children), it was found that the use of magnesium sulfate in pregnant women with threatened preterm birth for the purpose of fetal neuroprotection can postnatally reduce the incidence of CP. Prophylactic administration of antibiotics may increase the risk of developing CP in women who are in preterm labor with intact amniotic membranes and with the fetus in good condition during labor. Repeated doses of corticosteroids in pregnant women with threatened preterm birth have not shown a clear effect on reducing the risk of development of CP.[64] A recently published meta-analysis found that the use of magnesium sulfate prenatally in pregnant women with threatened preterm birth is very effective in reducing the incidence of CP in preterm infants postnatally.[84] In addition, an intervention that has a beneficial effect on the psychometric development of infants and on the development of vision and speech is the use of omega-3 polyunsaturated fatty acids in pregnancy and postnatally.[85,86] It is believed that the use of other micronutrients such as vitamin B12 and folic acid in combination with omega-3 fatty acids may have a beneficial effect on reducing the incidence of preterm birth in pregnant women and behavioral disorders in infants.[87]

Neonatal Interventions Affecting the Incidence of Neurodevelopmental Disorders

In a systematic review of 96 studies in 15,885 children, the following neonatal interventions were found to be effective in reducing the incidence of CP: therapeutic hypothermia in proven intrapartum hypoxia and the development of hypoxic-ischemic encephalopathy contributed to a reduction in the incidence of CP. Administration of methylxanthines (caffeine) in extremely immature infants, either mechanically ventilated or not, and methylxanthine administration prior to endotracheal extubation is neuroprotective.[31] In contrast, early postnatal administration of corticosteroids before the age of 8 days for chronic lung diseases contributed to an increase in the incidence of CP.[31] Postnatal procedures such as ethamsylate administration, volume expander administration, administration of collagen hydrolyzate instead of fresh frozen plasma, prophylactic administration of indomethacin, administration of synthetic surfactant, and prophylactic phototherapy did not affect the incidence of CP in preterm infants.[31]

New Published Data on the Continuity of Fetal to Neonatal Behavior

In the recently published paper, postnatal follow-up of fetuses with borderline and abnormal Kurjak's antenatal neurodevelopmental (KANET) scores are presented in Table 1[88] There were 153 fetuses with borderline scores and 52 fetuses with abnormal KANET scores, of whom 11 were terminated *in utero* or died postnatally, meaning that 41 could be evaluated postnatally.[88] In the group with borderline KANET scores, there were 145 with normal postnatal development, two had moderate, and four had severe developmental delay, while two fetuses died *in utero*. In the group of 52 infants with abnormal KANET scores, 26 had normal development, one infant had slight developmental delay, one moderate, and 13 infants had severe developmental delay, while 11 died *in utero*.[87] Severe developmental delay was more frequent in the group with abnormal KANET scores, which was highly statistically significant (Table 1; $X^2 = 315.28$; d.f. = 6; $p < 0.01$). Out of 1,102 children older than 2 years, 36 had abnormal and 11 borderline KANET scores.[88] Of 47 children with borderline abnormal KANET scores in one more than 3-year-old child CP was diagnosed.[88] Out of 1,556 children with normal KANET scores, 26 had developmental delay, of whom it appeared severe in 18.[89] One child from that group who had a normal KANET score developed severe developmental delay due to Kagami Ogata syndrome and is now 33 months old.[88]

Conclusion

Neurological assessment of fetus *in utero* is extremely difficult, even having such sophisticated equipment like 4D US. As it is well known that the quantity of GM is not so informative and predictive of neurological impairment, their quality should be assessed. "Gestalt perception" of premature GMs we are dealing with *in utero* and writhing GMs appearing 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.[57] 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 the optimality of CNS development.[34,37,71] Possibilities of 4D sonography are demonstrating the prenatal onset of brain damage, based on morphological and functional signs. There is no doubt that this observation is helpful, even though that prenatally observed signs are not yet highly predictive due to brain immaturity, their identification will be at least recognized as a retrospective marker for a prenatal insult.[88]

We now have applicable KANET screening neurological tests for the fetus, and assessment of a neonate is the continuation of that prenatal test, but standardized procedures for postnatal follow-up are still missing, because there are many neurological methods for postnatal evaluation, and many of them are too

Table 1: Postnatal follow-up of infants who as fetuses had borderline and abnormal KANET scores from low- and high-risk pregnancies including termination of pregnancy and postnatal death[88]

Name of the investigator (N)	*KANET score (N)*	*Postnatal developmental delay (N)*				
		No	*Slight*	*Moderate*	*Severe*	*Comment*
N = 482	Borderline N = 36	33	0	0	2	One IUD
	Abnormal N = 19	15	0	0	4	All severe congenital malformations
N = 520	Borderline N= 47	45	0	0	1	One IUD
	Abnormal N = 19	7	0	0	1[++]	Five died Six terminated
N = 212	Borderline N = 39	39	0	0	0	–
	Abnormal N = 6	3	0	0	3	One case of trisomy 13, 18, and 21
N = 60	Borderline N = 16	16	0	0	0	–
	Abnormal N = 2	1	1	0	0	IUGR one with slight developmental delay
N = 145	Borderline N = 3	0	0	2	1	–
	Abnormal N = 0	0	0	0	0	–
N = 26	Borderline N = 2	2	0	0	0	–
	Abnormal N = 1	0	0	0	1	One with severe delay Kagami Ogata syndrome
N = 35	Borderline N = 0	0	0	0	0	–
	Abnormal N = 1	0	0	1	0	IUGR
N = 17	Borderline N = 3	3	0	0	0	–
	Abnormal N = 1	0	0	0	1	Trisomy 18, died in the first day of life
N = 76	Borderline N = 7	7	0	0	0	–
	Abnormal N = 3	3	0	0	3	Two severe congenital malformations and one IUGR
Subtotal normal KANET	1351 (86.8%)	1348 (99.8)	0	2 (0.1%)	1 (0.1%)	One with severe delay Kagami Ogata syndrome
Subtotal borderline KANET	153 (9.8%)	145 (94.8%)	0	2 (1.3%)	4 (2.6%)	Two IUD (1.3%)
Subtotal abnormal KANET	52 (3.3%)	26 (50.0%)	1 (1.9%)	1 (1.9%)	13 (25.0%)	11 terminated or died (21.2%)
Total	1556 (100.0%)	1519 (97.6%)	1 (0.1%)	5 (0.3%)	18 (1.2%)	13 (0.8%)

X^2= 315.28; d.f. = 6; $p < 0.01$

[++]One infant with CP (with previous case of CP in the family); KANET, Kurjak antenatal neurodevelopmental test; N, number of infants; IUD, intrauterine death; IUGR, intrauterine growth restriction; d.f., degrees of freedom

complicated for everyday clinical use. The environment of prenatal and postnatal evaluation is quite different, which is the reason why the issue of longitudinal GMs assessment from prenatal to postnatal life is questionable and should be further investigated as *in utero*, we are dealing with quite a different environment and less mature brain. Could neonatal assessment of neurologically impaired fetuses bring some new insights into their prenatal neurological status is still unclear and to be thoroughly and prospectively investigated? A new KANET scoring system for prenatal neurological assessment of the fetus proposed by Kurjak et al. gives some new possibilities to detect fetuses at high neurological risk, although it is obvious that the dynamic and complicated process of functional CNS development is not easy to investigate. Although our journey of 15 years of investigating the KANET test could probably be positively evaluated, we still have a long way to go.

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