An Attempt to Discover Antenatal Etiological Factors for Cerebral Palsy: What does 3D and 4D Ultrasonography Add?

[1]Asim Kurjak, [1]Milan Stanojevic, [1]Ingrid Marton, [2]Mislav Herman, [3]Guillermo Azumendi

[1] Department of Obstetrics and Gynecology, Medical School, University of Zagreb, Sveti Duh Hospital, Zagreb, Croatia
[2] Department of Obstetrics and Gynecology, Medical School, University of Zagreb, Petrova Hospital, Zagreb, Croatia
[3] Ecographia Centro Gutenberg, Malaga, Spain

Correspondence: Prof Asim Kurjak
Department of Obstetrics and Gynecology, Medical School, University of Zagreb
Sveti Duh Hospital, Sveti Duh 64 Zagreb, Croatia
Tel. : + 385 1 3712319, Fax: + 385 1 3745534, e-mail : asim.kurjak@zg.t-com.hr

Abstract: Cerebral palsy (CP) is a nonprogressive condition affecting developing fetal or infant brain resulting in disorders of movement and posture which are sometimes accompanied by disturbances of cognition, sensation, perception, behavior and seizures. The incidence of CP being 2 to 2.5 per 1000 live births did not considerably change in the last decades. Improvement of perinatal care did not result in the decreasing prevalence of CP. Consensus Statement of International Cerebral Palsy Task Force and its modification presented the essential criteria to define an acute intrapartum event sufficient to cause CP. These criteria were not helpful in allocating the time of brain injury, proving that etiology of CP is difficult to investigate. Better markers of acute intrapartum injury should be defined, although much evidence exists that most causes of CP are prenatal. Advances in 3D and 4D ultrasound (US) give opportunities to investigate fetal morphology and behavior. By 4D US, head, body and limb movements can be visualized simultaneously. The earliest phase of development can be studied in detail, making 4D superior compared to 2D. Is applicable neurological test for fetus available? This question is complicated, because even postnatally several neurological methods of evaluation exist, while hardly accessible fetus has less mature brain. Inexistence of reliable neurobehavioral assessment method for the fetuses is discouraging. The scientific community should intensify efforts in finding out simple, clinically applicable, and reproducible fetal neurological test(s), with fair sensitivity and specificity.

Key words: Cerebral palsy, fetal behavior, 4D/3D ultrasonography, neurological assessment.

Learning objectives

- To introduce a basic knowledge of cerebral palsy (CP)
- To inform about obstetrical causes of CP
- To give an overview of the methods for the neurological assessment of the fetus by 4D ultrasonography.

INTRODUCTION

Cerebral palsy (CP) is a nonprogressive condition affecting developing fetal or infant brain resulting in different disorders of movement and posture which are sometimes accompanied by disturbances of cognition, sensation, perception, behavior and seizures.[1-4] It is defined as an "umbrella term covering a group of nonprogressive, but often changing motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of its development".[1-4] Together with autism and mental retardation, it is one of the three most common life long developmental disabilities.[3]

IMPORTANT FACTS ABOUT CEREBRAL PALSY: OBSTETRICAL POINT OF VIEW

The worldwide incidence of CP being 2 to 2.5 per 1000 live births makes it common condition, which incidence, as shown in the Figure 1, did not considerably change in the last thirty years.[5-7] Improvement of obstetrical and neonatal care did not result in the decreasing prevalence rate of CP. On the contrary, the incidence and severity of CP increased due to a better survival rate of very immature and tiny premature infants with significant morbidity and increased number of risk factors.[6,8] Little, who introduced the term cerebral palsy, advanced the hypothesis that the main causes of the condition were prematurity, asphyxia neonatorum and birth trauma. There is still widespread believe that adverse events in labor are responsible for development of CP and even more that those events are potentially preventable.[9] According to recent studies, most of the risk factors connected with development of CP are

prenatal, while delivery and intrapartum risk factors are considered to have minor role, as shown in the Figure 2.[10] As CP became the most important part of global childbirth litigation industry providing to the crisis of obstetrical care especially in developed countries, efforts have been made in order to better define an acute intrapartum events sufficient to cause CP.[9,11,12] According to the Consensus Statement of International Cerebral Palsy Task Force published in 1999, and its modification published in 2003, the essential criteria to define an acute intrapartum event sufficient to cause CP are given in the Table 1.[12,13] According to some publications, the most serious critics to the proposed criteria is that information about essential criteria are frequently missing from the medical records of children who were retrospectively investigated.[9] In another investigation none of the cases of CP born at term met all of the criteria for severe acute intrapartum hypoxia as a possible cause of CP.[14] In most cases, criteria clearly ruled out acute intrapartum hypoxia.[14] Nearly, 9% of the cases met the criteria for a severe metabolic acidosis at birth, and fewer than 20% of cases at term had early imaging evidence of an acute nonfocal cerebral abnormality.[14] On the other hand, many children with cerebral palsy have had one or more of the clinical signs which are widely assumed to reflect "fetal distress", but which may not represent acute intrapartum hypoxia.[9] The mentioned criteria were not helpful in allocating the time of brain injury, proving that etiology of CP is complex and difficult to investigate.[9,14] There is a need for better markers of acute intrapartum injury, although there is much evidence that most adverse events causing CP happen prenatally.[9,14] Major pathologies associated with CP are listed in the Table 2.[14]

Table 1: Criteria to define an acute intrapartum hypoxic event[13]

Essential criteria

1. Evidence of a metabolic acidosis in intrapartum fetal, umbilical arterial cord, or very early neonatal blood samples (pH < 7.00 and base deficit > 12 mmol/l).
2. Early onset of severe or moderate neonatal encephalopathy in infants born at 34 or more weeks of gestation.
3. Cerebral palsy of the spastic quadriplegic or dyskinetic type.
4. Exclusion of other identifiable etiologies, such as trauma, coagulation disorders, infectious conditions, or genetic disorders.

Criteria that together suggest an intrapartum timing (within close proximity to labor and delivery, for example, 0-48 hours) but by themselves are nonspecific for an asphyxial insult.

1. A sentinel (signal) hypoxic event occurring immediately before or during labor.
2. A sudden and sustained fetal bradycardia or the absence of fetal heart rate variability in the presence of persistent late or persistent variable decelerations, usually after a hypoxic sentinel event when the pattern was previously normal.
3. Apgar scores of 0-3 beyond 5 minutes.
4. Onset of multisystem involvement within 72 hours of birth.
5. Early imaging evidence of acute nonfocal cerebral abnormality.

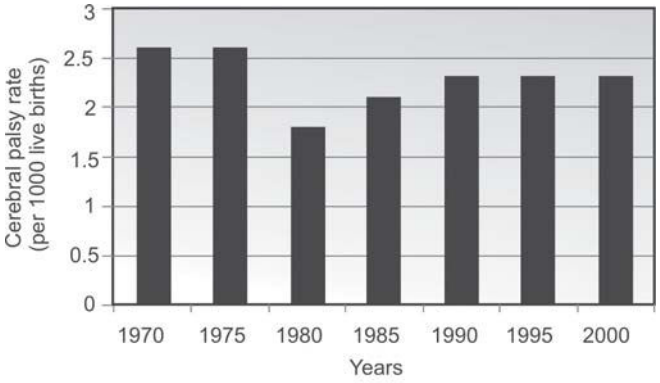


Fig. 1: Cerebral palsy rates per 1000 live births (1970-2000)[7]

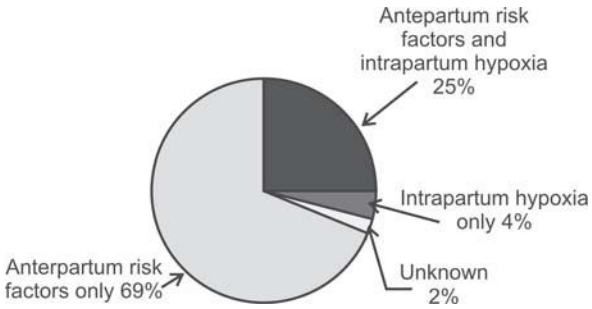


Fig. 2: Distribution of risk factors for newborn encephalopathy[10]

Table 2: Major pathologies associated with cerebral palsy[14]

- Prematurity
- Antepartum hemorrhage
- Complications of multiple pregnancy
- Genetic disorders
- Intrauerine infection; for example, chorioamnionitis, funisitis, villitis, cytomegalovirus, toxoplasmosis
- Intrapartum fever
- Intrauterine growth restriction
- Maternal and fetal coagulopathies
- Multiple congenital anomalies
- Maternal disease; for example, hypothyroidism, diabetes, drug abuse, severe pre-eclampsia, viral illness
- Placental pathology; for example, major infarction, thrombotic vasculopathy
- Tight nuchal cord
- Childhood causes
- Other causes; for example, fetal hemorrhage, rhesus disease.

THE DIAGNOSIS OF CP FROM OBSTETRICAL POINT OF VIEW

The detection 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.[15] Cerebral palsy does not result from a single event but rather there is a sequence

of interdependent adverse events providing to the condition.[16] This time frame of evolving adverse events is something which should be taken into account when thinking about the possibility of development of CP in infants.[15,16] The understanding of the profile of a child's disability across multiple domains is an ongoing process necessary for appropriate treatment and future planning.[15] This theoretical statement is sometimes very difficult to be practically implemented. Possible antenatal causes of neurological impairment are listed in Table 3.[12] An attempt to make early diagnosis of CP should be followed with factors related to pathogenesis, impairment and functional limitations in every patient.[15] In order to identify pathogenesis of the process, neuroimaging methods should be used, among which cranial ultrasound, magnetic resonance imaging, 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.[15] Impairment of organs or systems by clinical assessment of muscle tone, strength, control and 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 neurologic examination.[15,17] There is a possibility for the early 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 outcome.[18] As CP is a disorder of movement and postural control resulting in functional limitations, their detection could be helpful in detection of early impairment.[15] Clinical neurological assessment proposed and practiced by Amiel-Tison could be very helpful in the early detection of newborns at risk.[18]

In the last thirty years objective assessment of videotaped general movements (GM) by Precht's method has been shown to be predictive of later CP.[19] The quality of general movements at 2 to 4 months postterm (so-called fidgety GM age) has been found to have highest predictive value in the detection of the infants at risk for CP development.[20] It seems that assessment of the quality of GM is a window for early detection of children at high risk for developmental disorders.[20] Method is very simple and it is based on the so-called Gestalt evaluation of GM complexity and variation.[19,20] Assessment of GMs at 2 to 4 months postterm at so-called fidgety GM age has been found to have the highest predictive value for development of CP, if abnormal.[19,20]

Table 3: Factors that suggest a cause of cerebral palsy other than acute intrapartum hypoxia[12]

- Umbilical arterial base deficit less than 12 mmol/l or pH greater than 7.00
- Infants with major or multiple congenital or metabolic abnormalities
- Central nervous system or systemic infection
- Early imaging evidence of long-standing neurological abnormalities; for example, ventriculomegaly, porencephaly, multicystic encephalomalacia
- Infants with signs of intrauterine growth restriction
- Reduced fetal heart rate variability from the onset of labor
- Microcephaly at birth (head circumference less than a third of the centile)
- Major antenatal placental abruption
- Extensive chorioamnionitis
- Congenital coagulation disorders in the child
- Presence of other major antenatal risk factors for cerebral palsy; for example, preterm birth at less than 34 weeks' gestation, multiple pregnancy, or autoimmune disease
- Presence of major postnatal risk factors for cerebral palsy; for example, postnatal encephalitis, prolonged hypotension, or hypoxia due to severe respiratory disease
- A sibling with cerebral palsy, especially of the same type.

IS PRENATAL DIAGNOSIS OF NEUROLOGICALLY DISABLED FETUS POSSIBLE?

As the most factors providing to development of CP are prenatal, the eternal question is do we as obstetricians have means to detect fetuses at risk for development of CP early enough to protect them? So many difficult questions in only one sentence, hardly any answers. From the retrospective analysis of prevalence rates of CP in the last thirty years, we learned that there are no improvements in the obstetrical care which could enable early detection of CP.[4-7] Although in the last 20 years, it has been observed a shift in focus in the search for the origins of developmental disabilities and dysfunction from the intrapartum to antenatal period, there was no substantial improvement in the prenatal detection of potentially disabled babies.[21] The fact that no unified neurobehavioral assessment method of the fetuses currently exists is very discouraging and this fact should prompt the scientific community to intensify efforts in finding out such test(s) which should be simple, clinically applicable, and reproducible, with fair sensitivity and specificity. In order to achieve these goals, mentioned test should focus on gathering information that reveals neural continuity from fetus to newborn.[22,23] This statement is relying on the basic principle of development of nervous system which is continuing from prenatal to postnatal life. Early developmental periods are dominated by proliferative and migratory processes, while later, neuronal differentiation and synaptogenesis are prevailing.[22,23] Even harmful events during the first trimester can result in a variety of the CNS abnormalities, from severe neural tube defects to reduction of the number of neurons, which significantly reduces developmental potential.[24] The fetal neurobehavioral assessment focuses on fetal heart rate monitoring, assessment of fetal activity, behavioral state and responsivity to stimulation or biophysical profile.[21] Such assessment of the fetuses is still not sufficient to detect most of the fetuses at risk for development of CP, with very important

observation that prevalence rate of CP did not change substantially after introduction of all mentioned methods to clinical practice.

INVESTIGATION OF FETAL BEHAVIOR BY 2D ULTRASONOGRAPHY

The pioneer studies in the early 1980s of de Vries and colleagues have shown that the motor activity begins as early as the late embryonic period.[19,25] They have studied quantity and the quality of fetal general movements (GM), observed their rapid increase during the first trimester, and visualized new motor patterns.[19,25] Prechtl's school of fetal neurology described more than 20 years ago a large veriety of specific movement patterns emerging from 8 to 15 weeks of gestation, obtained by 2D sonography.[19,26] Movements are similar to those observed in neonatal period. That observation is confirming not only the continuity from fetal to neonatal period but also the maturation from fetus to neonate (from fetal to neonatal). Therefore, the qualitative assessment of GMs became part of fetal and neonatal neurological evaluation.[19,27] Since that time many new studies have been undertaken with precise description of different movement patterns, as well as their exact time of appearance during pregnancy.[28,29] Many studies have shown that already in the early stage of pregnancy, embryonic and fetal motor activity appears as spontaneous patterned activity, rather than just a random motion.[28-32] It has been observed that major movement patterns, usually develop and appear during the first trimester, explained by intensity of the motor development in this period of pregnancy.[33-35] Fetal movements between 9 and 12 weeks of gestation are characterized by changes of position and posture, and between 13 and 16 weeks changes of position are seen, as well as flexion and extension of the limbs. From 17th to 20th gestational weeks, fetuses are making slow flexion and extension of the trunk, sometimes accompanied by the movement of a single limb.[29] At that time fetuses perform isolated leg movements.[30] Progressive organization of fetal motor activity and its integration with other parameters of fetal activity into the fetal behavioral status occurs during second and third trimesters.[29,30,33]

3D AND 4D ULTRASONOGRAPHY IN THE ASSESSMENT OF FETAL BEHAVIOR

Recent advances in 3D and 4D ultrasonography provide us with new opportunities for the investigation of embryonic and fetal morphology and behavior.[26,36] With 4D sonography, head and body movements, as well as all four limbs and extremities can be visualized simultaneously in three dimensions.[37] Therefore, the earliest phase of anatomical and motor development can be observed and studied in detail, making 4D ultrasonography to be superior compared to 2D.[38,39] Body movements were found by 4D at 7 weeks of pregnancy, and limb movements at 8 to 9 weeks, which is a week earlier than by 2D.[40] It is important to mention that some of the movement patterns cannot be observed through all the pregnancy like startles and stretches which are observed only in the first trimester disappearing with the progression of gestational age. 4D allows observing hand movements and subtle fetal movements, such as facial mimics and expressions, like sucking and swallowing which could be much better visualized during the second and the third trimesters. Majority of mentioned expressions could not be visualized by 2D ultrasound.[41,42] 4D ultrasonography enables examination of fetal face with the awareness of a full range of facial expressions (Figs 3 and 4A and B), similar to those observed postnatally. In the study of Kurjak *et al* a reach repertoire of movements and facial expressions during the third trimester have been found and shown in the Table 4.[43] Fetal motility is considered not only to reflect the developing nervous system but also involves functional and maturational properties of fetal hemodynamics and the muscular system. The introduction of 4D ultrasonography was a turning point in the assessment of fetal behavior by providing the capability of simultaneous spatial imaging of the entire fetus and its movements.[33-35,41-51] As it was shown in our investigations, 4D has been used in establishing the standards of the quantity of GMs in different gestations, which is one step forward for the detection of fetal neurological test. Most types of movement patterns are present between 7 and 15 weeks of gestation.[47] Once observed, the movements remain unchanged throughout the whole pregnancy.[52] 4D US provided the possibility to study a full range of facial expressions including mouthing, grimacing, and eyelid movements (Figs 5A to C).[47-53] The definitions of types of analyzed movement patterns are presented in Tables 4 to 6, following the studies by de Vries and Prechtl.[52,54]

We studied fetal behavior in all three trimesters of normal pregnancy and noted a tendency toward decreased frequency of observed facial expressions and movement patterns with

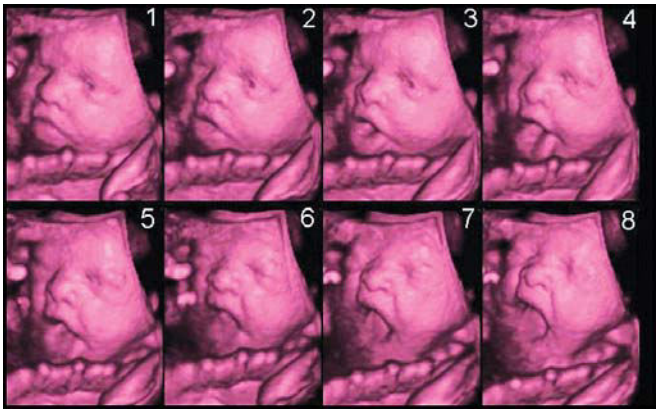


Fig. 3: 4D imaging sequences demonstrated isolated eye blinking parallel with tongue expulsion during third trimester of pregnancy

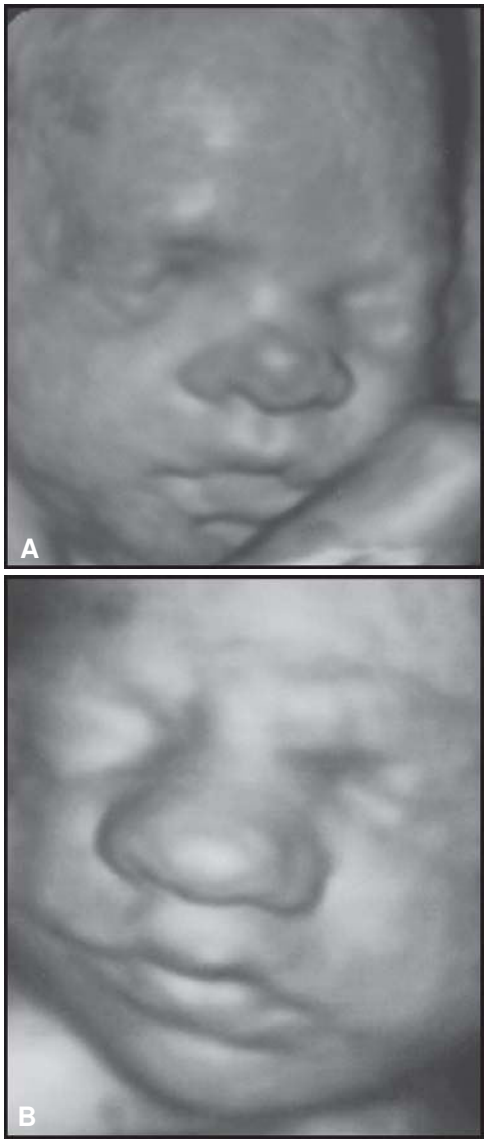


Fig. 4: Fetal face expressing emotions (speculates that these are sad babies)

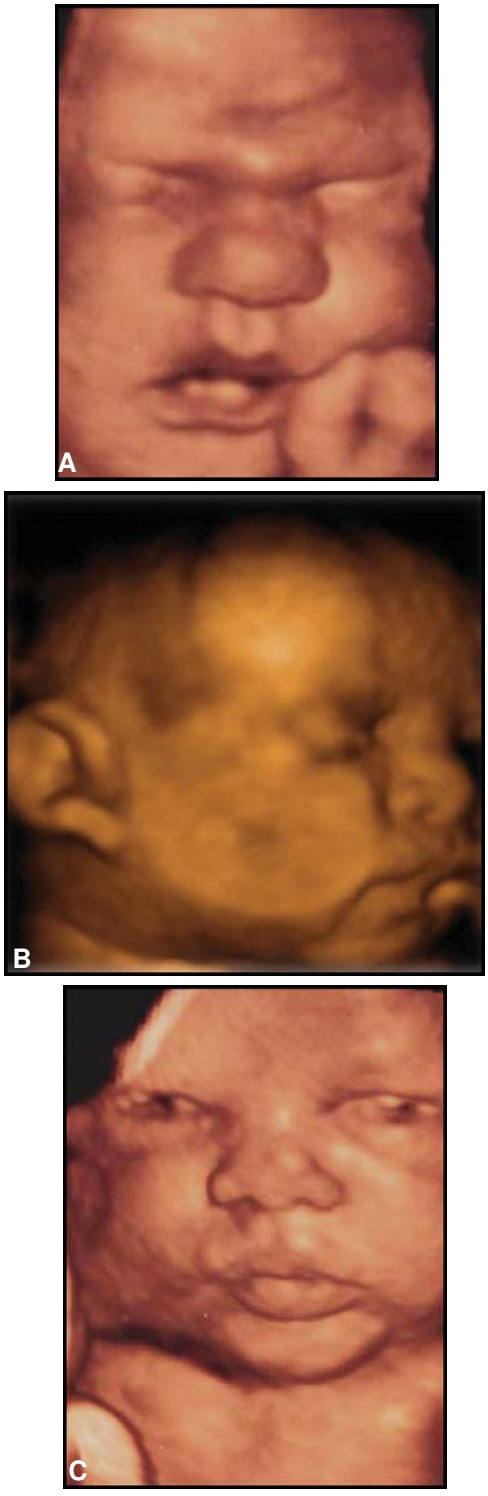


Fig. 5: Fetal face expressing mouthing (A), grimacing (B) and eyelid movements (C)

increasing gestational age.[53] In the longitudinal study, standard parameters of fetal movements and facial expressions in all trimesters of pregnancy were obtained and published.[53] Some illustrative examples of that work are presented in Figures 6 to 9. In first trimester, a tendency toward increased frequency of fetal movement patterns with increasing gestational age was noticed (Fig. 6). At the beginning of the second trimester, the fetuses began to display a tendency toward increased frequency of observed fetal facial expression to the end of second trimester. An oscillation and dispersion of the incidence of all facial expressions was observed, as seen in the polynomial regression diagram for yawning (Fig. 7). All types of facial expression patterns display the peak frequency at the end of second trimester, except in isolated eye blinking which began to increase at the beginning of 24 weeks of gestation because the fetuses cannot open the eyelids before this period. During the third

Table 4: Movements analyzed in embryos and fetuses in the first trimester[53]

• General movements
• Startle
• Stretching
• Isolated arm movements
• Isolated leg movements
• Head retroflexion
• Head rotation
• Head anteflexion

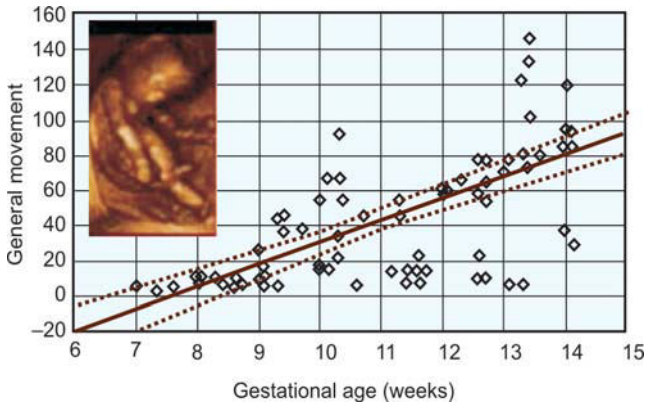


Fig. 6: The scatter plot and multiple regression analysis of the first trimester frequency of general movements *versus* the gestational weeks in the formula generating group

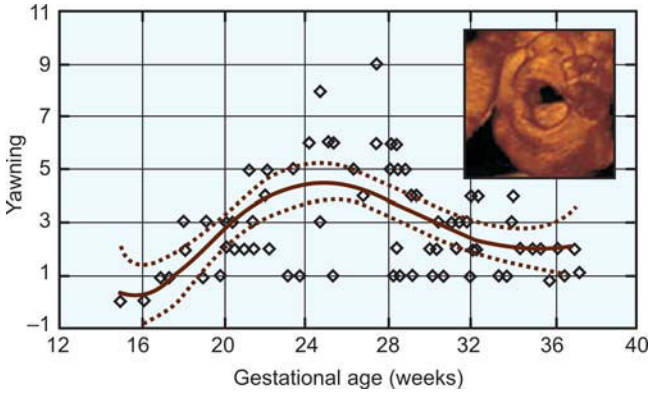


Fig. 7: The scatter plot and multiple regression analysis of the second and third trimesters frequency of yawning *versus* the gestational weeks in the formula generating group

trimester, the fetuses began to display decreasing incidence of fetal facial expressions. All types of head movements and hand to body contact , as well as hand movements indicate a tendency to decrease in frequency from the beginning of the second trimester to the end of third trimester (Figs 8 and 9).

Table 5: Movements analyzed in fetuses in the second and the third trimesters[53]

Facial expression	*Hand and head movements*
• Isolated eye blinking	• Head retroflexion
• Mouthing	• Head rotation
• Yawning	• Head anteflexion
• Tongue expulsion	• Hand to head direction
• Grimacing	• Hand to eye direction
• Swallowing	• Hand to mouth direction
	• Hand to face direction
	• Hand to ear direction

Table 6: Definition of some fetal movement patterns and facial expressions[25,52]

General movements	:	Series of movements with variable speed and amplitude, involve all parts of the body without distinctive patterning of body parts can be seen. Duration varies from a few seconds to about a minute
Startle	:	Quick generalized movements, starting in the limbs and spreading to the neck andtrunk, only last about one second
Stretching	:	A complex motor pattern, always carried out at a slow speed and consists of the forceful extension of the back, retroflexion of head, and external rotation and elevation of the arms
Isolated arm or legmovements	:	Rapid or slow movements, and may involve extension, flexion, external and internal rotation, or abduction and adduction of an extremity, without movements in other body parts
Head retroflexion, rotation and anteflexion	:	Isolated retroflexions, rotations and anteflexions of the head not associated with general movements. Usually carried out slowly, but they can also be fast and jerky
Hand to body contact: (head, mouth, eye, face, ear)		In this pattern of movement, the hand slowly touches the body parts, with extension and flexion of the fingers
Grimacing	:	The wrinkling of the brows or face in frowing
Isolated eye blinking	:	A reflex that closes and opens the eyes rapidly. Brief closing of the eyelids by involuntary normal periodic closing, as a protective measure, or by voluntary action
Yawning	:	Prolonged wide opening of the jaws followed by quick closure, with retroflexion of the head and elevation of the arms. This movement pattern is non-repetitive
Tongue expulsion	:	Facial expression characterized by expulsion of the tongue
Swallowing	:	Indicating that the fetus is drinking amniotic fluid. Swallowing consists of displacements of tongue and/or larynx
Mouthing	:	A facial expression characterized by mouth manipulation to investigate an object. Mouthing is most common in fetus and it may develop into a persistent, stereotyped behavior pattern.

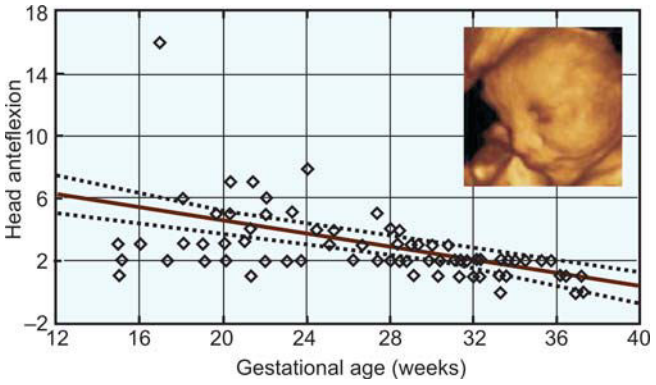


Fig. 8: The scatter plot and multiple regression analysis of the second and third trimesters frequency of head anteflexion versus the gestational weeks in the formula generating group

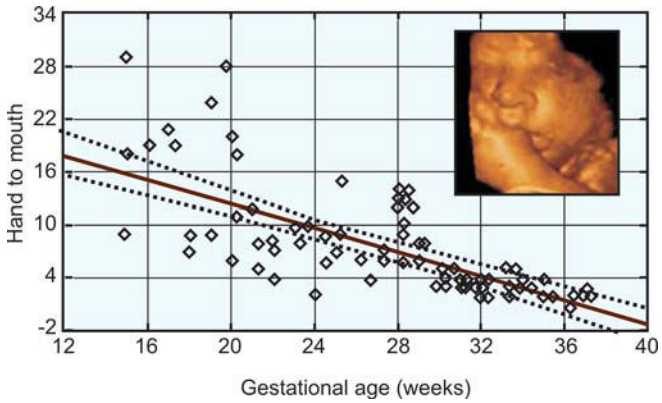


Fig. 9: The scatter plot and multiple regression analysis of the second and third trimesters frequency of hand to mouth movements *versus* the gestational weeks in the formula generating group

Quality of GMs Studied by 4D Ultrasound

As it was shown in postnatal studies of GMs, it is very important, besides the quantity, to study the quality of GMs as well.[19,20] From the postnatal studies we have learned that changes in the quality of movements are much more predictable for disability than their quantity.[19,20,55-58] There are still technical limitations of 4D equipment to assess quality of GMs, although the frame rate of 4D equipment is constantly improving.

Continuity 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 neurodevelopment disability than neurological examinations.[55] It is important to mention that postnatal observation of movement patterns was introduced by Prechtl and coworkers in the way that they have been observing spontaneous movements of the infant using video typing and "off-line" analysis of both quantity and quality of the movement.[56,57] They proved that assessment of general movements in high-risk newborns has significantly higher predictive value for later neurological development than neurological examination.[55,58,59] Kurjak and coworkers conducted a study by 4D ultrasonography and confirmed earlier findings made by 2D ultrasonography, that there is behavioral pattern continuity from prenatal to postnatal life.[50] Assessment of neonatal behavior is a better method for early detection of cerebral palsy than neurological examination alone.[60] 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 our ability of early detection of brain pathology. Early detection could possibly rise an opportunity to intervene and even prevent the expected damage.

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.[41,61,62] This new technology is not only a tool of fetal observation but also 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.[62,63] This information helps clinician in better interpretation of fetal movements. The experience acquired with the Amiel-Tison's Neurological Assessment at Term (ATNAT) helps us in interpretation of fetal movements.[64-66]

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 become differentiated at a very early age.[25] This means that we will take into a consideration period of pregnancy from 20 to 40 weeks of gestation, including the end of the neuronal migration and the post-migratory phase corresponding to the development of neocortex.[22,23]

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.[1-4] Motor disorders which occur in patients with CP are often accompanied by disturbances of sensation, cognition, communication, perception, and/or behavior, and/or with seizure disorder.[1-4] "Disturbances" is a term that refers to events or processes that in some way influence the expected pattern of

brain maturation.[66] Those events or processes are many, with consequences varying from very conspicuous to very subtle. It should be kept in mind what many neurologists emphasize, that morphology does not always correspond to neurological outcome.[64-68] The opposite view is the one from pediatricians and neurophysiologists, who are involved in long-term follow-up studies, and they are certainly not that optimistic. It would be wise to consider long run prognosis, for each specific type of fetal brain damage and make appropriate decisions for conservative management.

Hopes have been headed toward MR, but in many cases brain changes cannot be detected as early as the first year of life; for example, pathological gliosis which causes secondary hypomyelinisation.[64,65]

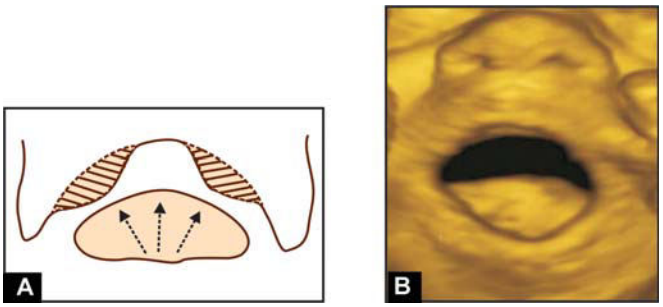
While examining the fetal head by 4D, sonographer should examine bony structures and fetal cranial sutures; if they are folding over one another, it is considered to be a bed sign previously described by Amiel-Tison.[64,65]

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*.[64,65] One of the possible signs detected could be high arched palate (Figs 10A and B), described by Amiel-Tison, in clinical assessment of the infant nervous system.[64,65] What was believed as undetectable became visible by 4D. Recently, the 3D "reverse face technique" has been described. This technique overcomes shadowing 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.[67,69]

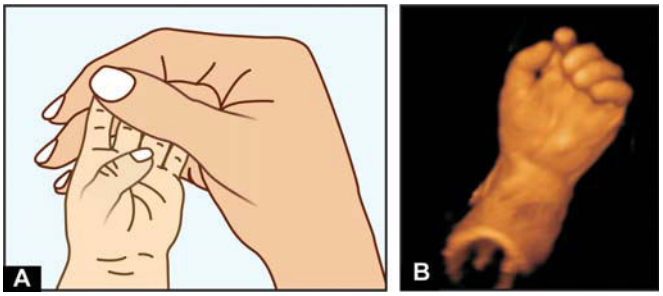
Pooh and Ogura examined 65 normal fetuses by 3D/4D. The purpose of their study was to investigate the natural course of fetal hand and finger positioning.[70] During 9th and on the beginning of 10th week, fetal hands were located in front of the chest and no movements of wrists and fingers were visualized.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

Amiel-Tison also described so called neurologic thumb squeezed in a fist (Figs 11A and B). Clenched fingers can also be detected by 4D sonography, as well as ovrlaping cerebral sutures (Figs 12A and B).[41,70]

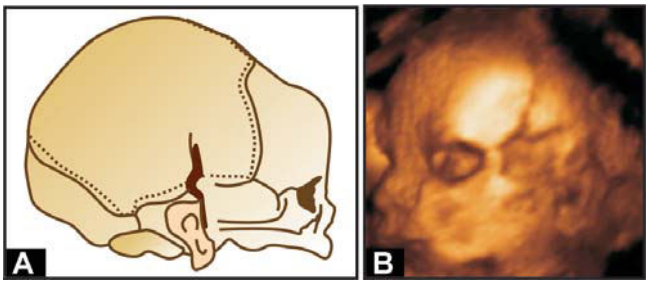
Head anteflexion becomes visible during 10th and 11th gestational weeks, according to de Vries and co-workers.[25] However, the activity of flexor muscles will depend on the upper system since 34 weeks of gestation. The absence of active head flexion explored by the raise-to-sit maneuver is one of the major neurological signs at 40 weeks of gestation.[18,65,66]



Figs 10A and B: High arched palate
(A. Scheme, B. 4D ultrasonography)[64,65]



Figs 11A and B: Neurologic thumb squeezed in a fist
(A. Scheme, B. Clenched fingers 4D USG)[64,65]



Figs 12A and B: Normal cranial sutures
(A. Scheme, B. Visualized prenatally by 4D USG pattern)[64,65]

CONCLUSIONS

Dipietro states that an emerging consensus recognizes the fact that "fetal neurobehavioral pattern reflects the developing nervous system"; however, we do not know yet the conceptual and methodological strengths and weaknesses of fetal assessments proposed.[21] We are not ready yet to predict the outcome inbetween two extreme situations, i.e. optimal or very abnormal. The predictive value for a favorable outcome of a complete neurobehavioral pattern in fetus as from 22 gestational weeks should be demonstrated. This is the goal of an on-going collaborative project by Kurjak *et al*.

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 of enormous help, 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.[64,65]

Are we approaching the era when there will be applicable neurological test for fetus? This question is still not easy 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. We have to publish proposal for fetal neurological test based on scoring of the quantity of GMs and some other signs.[71] We believe that it will fulfill its main task which is to find out fetuses at high neurological risk, but we still have a long way to go.

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