Intrauterine Growth Restriction and Cerebral Palsy

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SUMMARY
Intrauterine growth restriction (IUGR) can be described as condition in which fetus fails to reach his potential growth. It is common diagnosis in obstetrics, and carries an increased risk of perinatal mortality and morbidity. Moreover, IUGR has lifelong implications on health, especially on neurological outcome. There is a need for additional neurological assessment during monitoring of fetal well-being, in order to better predict antenatally which fetuses are at risk for adverse neurological outcome. Studies have revealed that the behavior of the fetus reflects the maturational processes of the central nervous system (CNS). Hence, ultrasound investigation of the fetal behavior can give us insight into the integrity and functioning of the fetal CNS. Furthermore, investigations carried out using modern method, four-dimensional (4D) sonography, have produced invaluable details of fetal behavior and its development, opening the door to a better understanding of the prenatal functional development of the CNS. Based on previous observations and several years of investigation, our research group has proposed a new scoring system for the assessment of fetal neurological status by 4D sonography named Kurjak antenatal neurodevelopmental test (KAneT). The value of KAneT in distinguishing fetal brain and neurodevelopmental alterations due to the early brain impairment in utero is yet to be assessed in large population studies. However, preliminary results are very encouraging. Key words: neurological risk, pregnancies complicated with IUGR.

1. INTRODUCTION
Fetal growth is a complex developmental process that involves anatomic changes over time. Intrauterine growth restriction (IUGR) can be described as condition in which fetus fails to reach his potential growth (1, 2). Cretan confusion is present in terminology associated with IUGR. By definition, 10% of infants in any population will have birth weights at or below the 10th percentile. IUGR could be manifest at a weight above the population determined at the 10th percentile (eg, an undernourished infant born at the 15th percentile whose genetic make-up would have place it at the 90th percentile). Distinctions between normal and pathologic growth often can not reliably be made in clinical practice. The use of terms IUGR and “small for gestational age” (SGA) has been confusing, and these terms often are used interchangeably (1). SGA and IUGR are not synonymous (3,4,5). SGA, is a different entity than IUGR, but is also associated with poor-perinatal outcomes. SGA is defined as a birth weight (BW) below a given (usually) the 10th percentile.
for gestational age. The term IUGR should be used only in regard to the fetus, whereas SGA should be used mainly in the newborn (but it can be estimated from sonographic measurements of the fetus) (2). IUGR is ideally detected by diminished growth velocity of the fetus on serial ultrasonographic scans (6). In this way, the function of growth becomes the object of interest instead of the result (i.e., birth weight).

There are several concepts of IUGR, and information on true IUGR is often missing from retrospective studies. The most common proxy for IUGR is small for gestational age (SGA). However, as it has been already mentioned, SGA is a heterogeneous category, including not only growth-restricted infants but also infants with chromosomal abnormalities, and small healthy infants as well. Many babies are simply genetically small and are otherwise normal (7). Some women have a tendency to have constitutionally small babies. There are at least three ways to obtain information on true intrauterine growth restriction: 1. by serial ultrasound estimates during pregnancies in which a decreased growth is detected; 2. by anthropometric measures postnatally; and 3. by using individualized or customized growth standards. Kurjak et al (8) illustrated two different patterns of IUGR that may be of significance for the short- and long-term prognosis of the fetus using antenatal ultrasonic assessment by measurement of fetal dimensions. They concluded that the late IUGR pattern is frequently associated with conditions that cause reduced placental perfusion, such as hypertension. A typical wasted look and low weight for height is the main characteristic of this group (8). In these fetuses, there is a predisposition to perinatal asphyxia and the Apgar score is low, with an increased brain-to-liver ratio. This type is probably the result of uteroplacental vascular insufficiency (8,9). The symmetric IUGR pattern, which occurs in 20% of SGA fetuses, results from prolonged growth impairment beginning early in the 2nd trimester, even from 18 weeks. There is a proportionate reduction in the fetal head, body length, and body weight, but growth does not generally stop. This type is not typically linked with hypertension or intrapartum asphyxia. Such growth failure has been realized in experimental animals by restriction of the mother’s protein or calorie intake (10). Some of these fetuses have genetic or chromosomal abnormalities and could be examples of reduced growth potential. Long-term follow-up of these fetuses has shown that prolonged IUGR causes stunting of growth in childhood and most likely up to adulthood, and a considerably reduced general development proportion (8).

2. CONSEQUENCES OF IUGR

Fetal growth restriction is one of most common complex problems in modern obstetrics. It is well known that IUGR can lead to significant fetal or neonatal complications. A number of studies have reported a 5–27% incidence of congenital abnormalities associated with IUGR, as compared with a 0.1–4% anomaly rate in control groups of normally grown neonates (11). The incidence of chromosomal abnormalities in IUGR infants is 4–5 times that of appropriate-for-gestational-age (AGA) infants (2% vs 0.4%); and intrauterine infection, especially cytomegalovirus, has been reported in 0.3–3.5% of IUGR infants (11). In addition, growth-restricted infants have up to an 8–10-fold increase in stillbirth and neonatal mortality (11). This, in part, is due to a higher incidence of hypoxia, asphyxia, meconium aspiration, and a generally poorer ability to tolerate labour with IUGR (11). Other developmental problems such as necrotizing enterocolitis, intraventricular hemorrhage (IVH), and neonatal encephalopathy, can also be related to IUGR. Those infants who survive the immediate perinatal period are still at risk for hypothermia, hypoglycemia, polycythemia, and other complications (11, 12). Animal studies have also shown an increased risk for cardiovascular and renal problems later in life (13). IUGR fetuses are connected with high rates of low ponderal indices at birth, hypoglycemia, and admissations to nurseries (7, 14).

In infancy, low birthweight is associated with childhood mortality from causes including infectious diseases and congenital anomalies, such as central nervous system and cardiovascular anomalies (15, 16). Numerous adult cardiovascular diseases, including coronary heart disease, hypertension, type II diabetes mellitus, dyslipidemia, and stroke, have been linked with low birthweight (17). The evidence for the link between risk of coronary heart disease and IUGR comes from the fact that it is independent of gestational age (18). SGA is connected with major psychiatric sequelae in later years. Birthweight less than 3 kg is linked with an increased risk of depression at age 26 years and over, in women but not in men (19). SGA is also connected with an increased risk of suicide and suicide attempts in later life (20). According to some data, severely IUGR fetuses suffer from intellectual impairment in the long term, particularly if neonatal management is less than adequate (14). Furthermore, as described by Jacobsson et al, (21) children with severe IUGR at term have an 8-fold higher risk of CP. These findings highlight the need for close antenatal monitoring of fetal growth (21). Moreover, it is essential to recognize these fetuses – and the earlier in fetal life, the better.

3. FETAL BEHAVIOR AND NEUROBEHAVIORAL ASSESSMENT

As early as possible, neonatologists try to identify neonates at risk of unfavourable neurodevelopmental outcomes. They are fairly reliably predicting very poor outcomes as well as optimal outcomes. However, within these two extremes, the prediction still re-
mains a challenge (22). Furthermore, there is a growing pool of evidence that many neurological disorders originate from intrauterine rather than perinatal or postnatal period. In addition, clinical and epidemiological studies have shown that encephalocerebral palsy (CP) most frequently results from prenatal rather than perinatal or postnatal causes (23). As the neuromotor system is the first to mature and cranial expansion passively follows hemispheric growth, neurologicalassessment should be able to produce early markers to predict later outcomes based on neuromotor and cranial findings. For many years, obstetricians have worked toward the same objective as neonatologists by monitoring fetal well-being during pregnancy. They rely on technical advances, namely ultrasonography (US) which has lead to the following statement: “Fetal behaviour can be defined as fetal activities observed or recorded with ultrasound equipment” (24). The advent of US has led to a kind of revolution. For more than 40 years, ultrasound has been extensively used in medical imaging, providing help for the diagnosis and staging of numerous diseases of different organs and systems of human body. The development of real time two-dimensional (2D) ultrasound has enabled the direct visualization of fetal anatomy and activity in utero. Analysis of the dynamics of fetal behaviour in comparison with morphological studies has led to the conclusion that fetal behavioural patterns directly reflect developmental and maturational processes of fetal central nervous system. Therefore, it was suggested that the assessment of fetal behavior and developmental processes in different periods of gestation may make possible the distinction between normal and abnormal brain development, as well as early diagnosis of various structural or functional abnormalities (25). However, 2D ultrasound was considered somewhat subjective method because information needs observer inter-
pretation. The latest development of three-dimensional (3D) and four-dimensional (4D) ultrasound that overcame some of the limitations of 2D methods enable precise study of fetal and even embryonic activity and behavior. Contrary to the 3D ultrasound which freezes the image of an object and therefore does not provide information on movements, 4D enables the opportunity of simultaneous visualization of the movements of the head, body, and all four limbs and extremities in three dimensions, in areal-time mode. 4D ultrasound or real-time 3D ultrasound makes it straightforward to comprehend some morphological dynamics, such as yawning, sucking, smiling, crying and eye blinking. This offers a practical means for assessment of neurophysiologic development, as well as for detection of anatomical pathology (26, 27). New diagnostic tool additionally provides possibility of spatial observation of fetal face, which was not provided by 2D sonography (28). 4D therefore allows the appearance and duration most of the each facial movement and expression to be determined and measured (Figure 1, 2).

In a relatively short period of time, 4D sonography has stimulated multicentric studies on fetal and embryonic behavior with more convincing imaging and data than those obtained by conventional ultrasonic and non-ultrasonic methods (Table 1 (29)).

The visualization of fetal activity in utero by 4D ultrasound could allow distinction between normal and abnormal behavioral patterns which might make possible the early recognition of fetal brain impairment (30, 31). As it is not yet possible to assess functional development of the CNS directly, investigators have started to analyze fetal behavior as a measure of neurological maturation including properties of fetal hemodynamics and the muscular system, as well (32). US technique allowed the investigation of spontaneous fetal motor activity in utero. Since fetal body movements give important information about the condition of the fetus, their quantitative as well as qualitative aspects were analyzed. For many years the interest of obstetricians was focused on the quantity of fetal movements which was considered as an indicator of fetal well-being. Later studies on the subject have shown that movement counts are poor indicator of brain damage, mainly because the great intra- and inter-individually differences and the large overlap between normal and abnormal, which makes this method clinically useless. On the other hand, changes in the elegance and fluency, as well as the variability and fluctuation of intensity and speed of motor performances were shown to be prominent in the sick preterm infants. It became evident that the qualitative changes in motor patterns of both the fetus and neonate precede quantitative changes when the integrity of the nervous system is impaired. It must be admitted that it is more difficult to objectify complex qualitative changes than
it is simply to count certain events when they occur, but the Gestalt-perception is an excellent method for dealing with such phenomena. Important step is videorecording of movements of sufficient length to make a selection of several movements from one recording session. The observed general-movements are diagnosed as normal if the movements are complex; including neck, trunk and limb movements in a variable sequence, and are fluent and wax and wane in their intensity. GMs are selected for judgement only if they last for 20 seconds or longer. If the GMs are monotonous, have less complexity and are repetitive in pattern, they are judged as abnormal and as being of “poor repertoire”. Other abnormal patterns are the “cramped-synchronised” type, when the movements are occurring en block and generalized muscle contraction and relaxation appear almost simultaneously, or the movements may occur in a jerky and exaggerated manner and in chaotic order. If the movements last very shortly and hence, they are difficult to be judged then we speak of “hypokinesis”. Several studies employing this new assessment have been carried out and they showed that the early normal or abnormal findings of the GM quality are highly predictive for later outcome (33, 34). Assessment of GMs is based on the concept of ontogenetic adaptation corresponding to the development of a human organism, which is during each developmental stage adapted to the internal and external requirements. Prechtl stated that spontaneous motility, as the expression of spontaneous neural activity, is a marker of brain proper or disturbed function (23, 35). The observation of the 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. All endogenously generated movement patterns from an unstimulated central nervous system could be observed as early as from the 7 to 8 weeks of postmenstrual age, with a reach repertoire of movements developing within the next two or three weeks, continuing to be present for 5 to 6 months postnatally. The identification of “CNS depression” during fetal life is based on pre-competences (opening of the eyes, variety of facial expressions), primary reflexes (rhythmical bursts in the sucking pattern) and quality of GMs (34, 36, 37). The addition of cranial signs (such as insufficient head growth and overlapping sutures) to neurological signs could be a valuable complement (34, 36). Moreover, the identification of dynamic and static patterns of the symptoms may be as helpful to date the insult as it is postnatally: the more stable the signs, the more precise is the timing of the insult. In the presence of neurological signs in fetuses, the next step is to proceed to the clinical synthesis. In order to do so, all examined should be followed till the age of two years, when their categorization into disabling or non-disabling CP can be possible, based on clinical neurological findings and presence or absence of the ability to walk. Obstetricians would have a great benefit if it were possible to assess the condition of the fetal nervous system especially due to the fact that in many cases obstetricians are held responsible for brain damage in neonates, regardless of a growing pool of evidence that most of such damages are consequences of perinatal complications. Even after the fetal brain anatomy can be visualized by ultrasound and the development of the fetal brain is well understood, not much is known.
about the functional development of the fetal CNS. In other words, the fetal CNS is not accessible. It is possible only to ascertain the output of the CNS, i.e. ‘fetal behavior’. Observation of fetal behavior provides indirect assessment of the most important human organ. It is possible to look closely at the functioning of the CNS and the brain. Prenatal motility is considered to reflect the developing nervous system but also involves functional and maturational properties of fetal hemodynamic and therm muscular systems (38). Prechtl and his coworkers (39) have explored spontaneous motility during human development. They introduced the concept of ontogenetic adaptation, meaning that during each developmental stage, the functional organization has to take into account internal and external requirements. Any fetal brain damage will interfere with endogenous motor activity. Therefore, spontaneous movements, as an expression of neural activity, could be used as a marker for fetal brain status. Consequently, the observation of the unstimulated fetus or infant should contribute significantly to the assessment of central nervous system (CNS) function. Even after delivery, behavioral patterns frequently provide the most useful indicators of brain function in spite of having extending access to neurological, physiological and pharmacological measures (38). This remarkable continuity of endogenously generated activity from prenatal to postnatal life may allow identifying those fetuses and infants with emerging neurological impairment. During the nine months of gestation, the repertoire of fetal activities constantly expands, correlating precisely with structural development of the CNS (40). Major developmental events, such as the establishment of neural connections in different regions of the brain, are accompanied by the occurrence of new patterns of fetal activity or with the transformation of the existing patterns. The organization of behavioral states during the final weeks of pregnancy shows that the connection between cerebral cortex and periphery is established, and that the cerebral cortex takes control over fetal activity. This also indicates the ability of the fetus to perceive and process external signals. Furthermore, the latest results indicate that even higher brain functions, such as learning, develop in utero during the last weeks of gestation (40). The major problem with the study of fetal behavior is that it is very time consuming and not enough functional for routine clinical practice. The question of subjectivity should be overcome using recording of information. Nevertheless, there is no other possibility of assessing the function of the CNS in utero, and this is needed for understanding the hidden information in the neurodevelopmental pathways of the fetal CNS. Only if normal behavior is fairly understood, is it possible to identify and to perceive abnormal behavior before birth (28, 41). First reports on fetal behavior obviously suggested that these studies should be standardized as much as possible. An objective analysis with strict application techniques and the use of valid reference ranges appropriate for the gestational age are essential (32). Without such standardization, comparisons with former or future measurements of patients and comparable studies cannot be made. In order to achieve this goal the Zagreb group published the first study which described the 4D sonographic techniques used for obtaining longitudinal standard parameters of fetal neurological development in all trimesters of anormal pregnancy (42). Measurement of 7 parameters in the 1st trimester and 11 parameters in the 2nd and 3rd trimesters correlated with gestational age. Those parameters have been followed longitudinally through all trimesters and showed increasing fre-

<table>
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<tr>
<th>Author</th>
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<tbody>
<tr>
<td>Kuno et al</td>
<td>2001</td>
<td>Provided a novel means for evaluation of fetal behavior in the early second trimester of pregnancy.</td>
</tr>
<tr>
<td>Kurjak et al</td>
<td>2002</td>
<td>Improved visualization of details of the dynamics of small anatomical structures, body and limb movements can be visualized a week earlier than with conventional 2D-US.</td>
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<tr>
<td>Kurjak et al</td>
<td>2003</td>
<td>Enhanced determination of exact direction of the fetal hand and improved assessment of complex fetal facia movement and expression.</td>
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<td>Kurjak et al</td>
<td>2004</td>
<td>Enhanced assessment of fetal behavior, and proved continuation from fetal to neonatal behavior.</td>
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<tr>
<td>Hata et al</td>
<td>2005</td>
<td>Provided novel means for evaluation of fetal movement, particularly fetal facial expression, in the second and third trimesters.</td>
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<tr>
<td>Kurjak et al</td>
<td>2005</td>
<td>Enhanced depiction of different facial expressions and movements, which might represent fetal awareness.</td>
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<tr>
<td>Andonotopo et al</td>
<td>2005</td>
<td>Both 2D and 4D methods are required for the assessment of early fetal motor development and motor behavior.</td>
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<tr>
<td>Kurjak et al</td>
<td>2005</td>
<td>Reviewed antenatal development of fetal behavioural patterns</td>
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<tr>
<td>Salihagic et al</td>
<td>2005</td>
<td>Reviewed a significant advance in studying fetal behavioral patterns and understanding structural and functional development of fetal CNS.</td>
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<tr>
<td>Kurjak et al</td>
<td>2006</td>
<td>First paper on longitudinal assessment of normal neurobehavioral development by 4D-US.</td>
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<tr>
<td>Yigit et al</td>
<td>2006</td>
<td>Prospective randomized study on fetal facial expressions and fetal movement patterns in all three trimesters.</td>
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<tr>
<td>Yan et al</td>
<td>2006</td>
<td>4D analysis of fetal facial expression early in the third trimester.</td>
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<tr>
<td>Morokuma et al</td>
<td>2007</td>
<td>First simplified ultrasound screening for fetal brain function based on behavioral patterns.</td>
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<tr>
<td>Kurjak et al</td>
<td>2007</td>
<td>New scoring system for fetal neurobehavior assessed by 3D and 4D-US.</td>
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Table 1. Additional findings of fetal behavior by 4D ultrasound in published reports. (From 29)
quency of fetal movements during the first trimester. A tendency towards decreased frequency of facial expressions and movement patterns with increasing gestational age from second to third trimesters has been confirmed (43). Despite the longstanding conclusion that it is possible to make valid conclusion about brain function from observed, no generalized antenatal behavior screening has been developed to identify fetuses that may have central nervous system defects. Recent study from Morokumatried to produce screening test that would be less time consuming and in that way cost effective as compared to their previous study (43). They devised a brief ultrasound examination to distinguish fetuses with compromised central nervous system function from the general population and evaluated it with their study (44). The study designed compared findings on five behavioral patterns obtained by retrospectively reviewing the ultrasound examinations of 5 fetuses that had abnormal behavior with prospectively obtained findings of 2 normal fetuses. Median time for brief examination criteria was 50 minutes (range 30 to 60 minutes) with the only case undetectable by this brief ultrasound examination had an eye-movement period significantly longer than the normal upper limit. Improvements in technology and procedures that provide direct access to the fetus in utero are generating the impetus for prenatal developmental research to move beyond the simple documentation that behavior abnormalities during pregnancy can produce effects that are evident in their offspring after birth. In other words, behavioral study of the fetus will be necessary to understand the origins of motor and sensory capabilities of infants and the mechanisms of altered developmental outcomes (36). Awareness of changing risk, and the potential for significant neurodevelopmental problem, is an underlying principle of perinatal medicine. Unfortunately neuroanatomical outcomes often result from a delay in recognizing or responding to CNS developing risk. This factor may necessitate the timely referral of individuals to an appropriately staffed facility. The timing of referral can be critical but, there are obvious difficulties which may result in the decision to refer being considered unnecessary, or on the other hand, too late.

4. FETAL BEHAVIOR IN PREGNANCIES COMPLICATED BY INTRAUTERINE GROWTH RESTRICTION

Studies dealing with fetal behavior in IUGR pregnancies are presented in Table 2 (45). One of the first studies on the impact of growth restriction on the fetal behavior focused on fetal breathing and on the course of behavioral state (46). To achieve that goal, Van Vliet and his group used real-time ultrasound scanners to detect fetal eye, body, and breathing movements, and the fetal heart rate of 12 growth-retarded fetuses between 36 and 40 weeks of gestation. The mean incidence of fetal breathing was greater during periods of fetal activity (body and eye movements present, greater heart rate variability) than during quiescence (body and eye movements absent, narrowed heart rate variability) at all gestational ages studied in both low-risk and growth-retarded fetuses. During periods when one of the state variables was initiates active condition while the other two were quiet, or the reverse, the incidence of fetal breathing was intermediate between those found when all three state variables were in agreement. After behavioral states had developed, at 38 and 40 weeks, the mean incidence of fetal breathing in the low-risk fetuses was greater during active states than during the quiet state. There was no apparent increase in the degree of linkage between fetal breathing and other expressions of fetal activity after the emergence of behavioral states (46). In another study by the same group, behavioral state observations were carried out on 12 fetuses which subsequently had birth weights below the 10th percentile (47). The gestational ages at the time of study ranged from 32 to 40 weeks. Real-time ultrasound scanning was used to detect fetal body and eye movements, and the fetal heart rate was continuously recorded using acclinal fetal monitor. The appearance of states seemed to be delayed in the growth-restricted fetuses since states were present in only three of eight growth-restricted fetuses studied at 40

<table>
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<tr>
<th>Author</th>
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<th>Main findings</th>
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<tr>
<td>Van Vliet</td>
<td>1985</td>
<td>Results on relationship between fetal activity and behavioral states in the third trimester growth-restricted fetuses</td>
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<tr>
<td>Van Vliet</td>
<td>1985</td>
<td>Showed that the quality and quantity of the growth-restricted fetal motility is disturbed</td>
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<tr>
<td>Arduini</td>
<td>1988</td>
<td>Showed that the quality and quantity of the asymmetrical growth-restricted fetal motility is disturbed</td>
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<tr>
<td>Rizzo</td>
<td>1987</td>
<td>Findings on the influence of fetal blood flow on the IUGR fetal motility</td>
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<tr>
<td>Sival</td>
<td>1992</td>
<td>Findings on the IUGR influence on the fetal general movements</td>
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<tr>
<td>Ribbert et al</td>
<td>1993</td>
<td>Showed the dynamic of fetal movements and relations to other parameters of fetal well-being in growth-restricted fetuses</td>
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<tr>
<td>Vindla et al</td>
<td>1997</td>
<td>Findings on fetal movements as the predictor of fetal condition</td>
</tr>
<tr>
<td>Bekedam et al</td>
<td>1991</td>
<td>The effects of maternal hyperoxia on fetal breathing movements, body movements and heart rate variation in IUGR fetuses</td>
</tr>
<tr>
<td>Andonotopo et al</td>
<td>2006</td>
<td>4D findings on fetal behavior of growth restricted fetuses.</td>
</tr>
</tbody>
</table>

Table 2. Additional findings of fetal behaviour in high risk-IUGR pregnancies in published reports. (From 45)
weeks. Also at 40 weeks, the proportion of discordant association of the state variables was increased in the growth-restricted fetuses as compared to the control. There were no consistent differences between the two groups in the occurrence of defined combinations of parameters of the state variables at earlier ages. The results from this study showed that the growth restricted fetuses have impaired quality and quantity of somatic motility in comparison to low risk fetuses of equivalent gestational age. These observations suggest that some aspects of central nervous system function are disturbed in growth-retarded fetuses, even in the absence of fetal distress [48]. Since asymmetrical intrauterine growth restriction occurs earlier than symmetrical or combined one it was important to study the fetal behaviour in the group of fetuses that develop growth restriction in earlier gestational age. For that purpose the behaviour of 15 asymmetrical intrauterine growth restricted fetuses was compared to that of a control group of healthy fetuses by simultaneous cardiotocographic and ultrasonographic examinations [48]. Behavioural states analysis was carried out according to Nijhuis et al. [49] and fetal movements were automatically synchronized with fetal heart rate (FHR) and grouped for each fetal heart rate pattern (FHRP). There were no statistical differences in the distribution of FHRP between healthy and IUGR fetuses. On the other hand quantitative differences were found when the movements investigated were related to FHRP. Moreover IUGR fetuses showed a reduction of state 1F (quiet sleep) and an increase of periods of no coincidence between behavioural state variable when compared to the control group fetuses. These findings, therefore, suggest the existence of quantitative differences in fetal behaviour in asymmetrical IUGR fetuses when compared to healthy fetuses [48]. To see whether these differences were caused by the compromised vascularization the degree of vascular peripheral resistance was evaluated by means of pulsed doppler ultrasonicequipment in the group of asymmetrical growth restricted fetuses and in control group [50]. All fetuses underwent simultaneous cardiotocographic and echographic examinations for two consecutive hours at 36–38 weeks of gestation. The distribution of gross fetal body movements, fetal breathing movements and fetal eye movements was analysed during the different fetal heart rate patterns. Furthermore, the incidence and organization of fetal behavioural states was investigated. Growth restricted fetuses were divided into two groups: the basis of the presence or absence of end diastolic flow in the fetal thoracic descending aorta. The results were in accordance with previous findings that growth restricted fetuses showed a delay in the integration of behavioural patterns and a lower coincidence of behavioural states. These findings are particularly evident in the fetuses with a severe increase of peripheral vascular resistance (absence of end diastolic flow in descending aorta) suggesting that a delay in central nervous system development is present in asymmetrical growth retarded fetuses and that there is a possible relationship of this delay to the degree of peripheral vascular resistance. Since general movements are considered to be an important for prediction of fetal neurobehavior next step was to study the effect of severe intrauterine growth restriction on its quality [51]. The study was performed longitudinally in 17 human fetuses and fetal movements were recorded by means of weekly 1 h ultrasound and video registrations, following by neurological examinations after birth. No clear effect of uncomplicated intrauterine growth restriction could be detected on the quality of general movements, but the quality was disturbed. General movements became slow and small in amplitude in cases where there was a reduction in the amount of amniotic fluid. Parallel to the onset of abnormal fetal heart rate patterns, general movements became poor in repertoire, while they were hardly discernible after further deterioration of the fetal condition. With the exception of 3 infants with cerebral haemorrhage, the quality of general movements observed just before after birth was identical. In these infants, the quality of general movements as well as the results of the standardized neurological examination tended to normalize at 3 months and 1 year, respectively. This study showed that in contrast to prenatal period uncomplicated IUGR had no marked effect on the quality of general movements or the results of the neurological examination at the age of 1 year [51]. In another study by the same group 17 fetuses with intrauterine growth restriction (IUGR), the quantity of general movements and fetal breathing movements were studied both cross-sectionally and longitudinally [52]. In IUGR fetuses, cross-sectional comparisons were made between the quantity of fetal movements and the fetal clinical condition and the quality of general movements. In addition, the quantity of fetal movements in IUGR was compared with that in uncomplicated pregnancies and in pregnancies complicated by premature rupture of the amniotic membranes. In IUGR, the quantity of general movements declined from 25 weeks gestation onwards, whereas the quantity of fetal breathing movements increased. Longitudinal assessment of these parameters was obtained in four cases and showed a decline of general movements. No relationship between prenatal longitudinal data and neonatal outcome could be observed. The quantity of general movements was also that of breathing movements was low in IUGR group with abnormal fetal heart rate patterns compared to group with normal parameters. In group with reduced amount of amniotic fluid only the quantity of
breathing movements and not of
general movements was slow. A
similar pattern was found in the
relation with the quality of general
movements observed during fetal
deterioration. Cross-sectional anal-
ysis of median values (28–31
weeks gestation) did not reveal dif-
fferences in the quantity of gen-
eral movements when IUGR, nor-
mal pregnancies and premature
rupture of the membranes (with
or without oligohydramnios) were
compared. The quantity of fetal
breathing movements was signifi-
cantly lower in pregnancies com-
pli cated by IUGR and by prema-
ture rupture of the membranes
with oligohydramnios compared
to those of normal pregnancies
and premature rupture of the
membranes without oligohydram-
nios. In uncomplicated IUGR,
the quantity of general movements
and breathing movements was in
the same range as in normal un-
complicated pregnancies. Similar
to the quality of general move-
ments, the quantitative variables
were related to the fetal condition.
However, in contrast to the quali-
ty of general movements, the
quantity of general movements
and breathing movements showed
a high inter- and intra-individual
variation. Therefore, the results of
this study discouraged the use of
quantitative aspects of general
movements and breathing move-
ments as reliable indicators of the
neurological condition in the indi-
vidual fetus (52). On the other hand,
Ribbert and coworkers showed that
the assessment of fetal activity may
be of help in fetuses with a marginally reduced
FHR variation, in which prolonga-
tion of pregnancy is considered
desirable to allow further matura-
tion in utero (53). In order to de-
termine changes occurring with
time they longitudinally studied
fetal heart rate variation, general
movements, breathing movements
and haemodynamics in unin-
trauterine growth restricted
fetuses, who eventually were de-
ivered by caesarean section (CS)
because of fetal distress. In 14 of 19
fetuses abnormal velocity wave
forms were present from the be-
inning of the study onwards. FHR
variation was initially just within
or below the norm and fell further
during the last 2 days before CS.
General movements and breathing
movements fell below the normal
range later and in slower rate of
occurrence than FHR variation.
Fetal GM showed a more or less
consistent fall in time, whereas fe-
tal breathing movements (FBM)
showed a wide range through-
out the period of observation.
The poorest outcome occurred in fe-
tuses with reversed end-diastolic
velocities and rapid fall in FHR
variation. It was concluded that
with progressive deterioration of
the fetal condition abnormal ve-
locity wave form patterns occur
first; FHR variation is reduced sub-
sequently while GMs and FBM are
the last to become abnormal (53).
In another study fetal heart rate
variation (FHRV) and movements
(FAM) was investigated in 27
normally grown fetuses and in 18
fetuses with intrauterine growth
restriction (54). The results
confirmed previously shown
decrease of fetal movements in
IUGR fetuses as compared to nor-
mally grown fetuses at all gesta-
tion times. The investigators re-
ported that IUGR fetuses also
spent a significantly lower pro-
portion of time exhibiting high FHR
variation at 28–31 weeks. If the fe-
tal movements were compared to
FHR one can conclude that more
of the IUGR fetuses had abnormal-
ities of movements. Finally, within
the IUGR fetuses, those with small
head circumferences (less than
3rd centile) had lower movement
rates during periods of both low
and high FHR variation, though
this was only statistically signifi-
cant for periods of low FHR vari-
ation. This published report of-
fered the possibility that objec-
tive evaluation of fetal condition
which could be used in a clinical setting
and could provide a more sensitive
method of fetal assessment than
biophysical profile scores (54). A
causal relationship with the im-
pairment of fetal oxygenation has
been suggested for a reduction in
the incidence of fetal movements
and in fetal heart rate variation. To
test these hypotheses, 16 IUGR fe-
tuses and 13 normally grown fetu-
es were observed during maternal
hyperoxygenation that was ap-
plied for 40 min in order to in-
crease fetal PO2 levels (55). All
IUGR fetuses had abnormal Dop-
pler blood velocity waveforms of
the umbilical artery suggesting an
impaired uteroplacental exchange.
The effect of hyperoxygenation on
fetal breathing and body move-
ments and on fetal heart rate was
evaluated. In the IUGR fetuses
there was a significant increase in
fetal breathing and body move-
ments and in heart rate variation
during hyperoxygenation as com-
pared to the preceding control pe-
riod of 40 min. No significant
changes in fetal breathing and
body movements were found in
the normally grown control fetu-
es. A surprising observation was
the increase of the number of
heart rate decelerations after dis-
continuation of the maternal hy-
peroxygenation. It was concluded
that in IUGR fetuses the increase
in fetal heart rate variation and
the increase in the incidence of
breathing and body movements
during maternal hyperoxygen-
ation substantiates the relation-
ship between these variables and
the oxygenation status of the fe-
tus. The implementation of 4D
sonography was necessary to find
out whether the quality of fetal
facial expression and quality of
body movements can be used as
an additional diagnostic criterion
for prenatal brain impairment in
fetuses with growth restriction.
For that purpose, a retrospective
study was conducted in 50 preg-
nant women with a growth-re-
stricted fetus and in 50 uncompli-
cated healthy women in the
third trimester of pregnancy (56).
4D ultrasound observation was
specifically used to assess wheth-
er functional brain impairment
and fetal growth restriction had
prenatally occurred by the utiliza-
tion of several behavioral patterns.
The results showed that the medi-
an value of all movement patterns

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in the normal fetuses differed from fetuses with intrauterine-growth restriction (IUGR). Statistical evaluation revealed significant differences in the distribution of the movements between these groups. A tendency that IUGR fetuses have less behavioral activity than normal fetuses was noted in all observed movement patterns. Correlation reached statistical significance between normal and IUGR fetuses in the third trimester in hand to head, hand to face, and head retroflexion. Statistically significant differences could be shown in the distribution of the median values of observation over the five qualitative categories of head and hand movements. Using 4D sonography, this study has opened for the first time the possibility of visualizing the full range of facial expressions in the IUGR condition. The median frequency of all facial expressions in the IUGR group was slightly lower compared with the control group. These recent data on IUGR fetuses obtained by 4D sonography are stimulating and might result in a more effective strategy to assess development before birth and may encourage future use of 4D ultrasound for quantitative and qualitative assessment of fetal behaviors possible indicators of the neurological condition in IUGR fetuses (56).

5. IUGR AS AN ANTENATAL RISK FACTOR FOR CEREBRAL PALSY

IUGR entails an increased risk of neonatal morbidity and mortality and also seems to affect brain development (57, 58). Some specific alterations in the brains of IUGR infants, including restriction of the volume of gray matter, a reduced amount of total DNA in glial cells and neurons, and changes in cerebral hemodynamics, have been reported (59). This is also supported by animal studies showing the reduced oxygen delivery to the brain and restricted growth of the forebrain and cerebellum (60). Moreover, it has been established that infants who are somewhat heavier at birth than is average for their gestational age and gender are at the lowest risk of having cerebral palsy and the lowest risk of perinatal death (61, 62). This optimum birth weight for best outcomes seems to be about one standard deviation (SD) heavier than the average birth weight for gestational age among healthy infants. At all gestations, infants who are either smaller or larger than this optimum size have a progressively increased risk of cerebral palsy (63). Furthermore, the frequency of cerebral palsy and the relative severity of the cases also increase away from the same optimum weight for gestational age (62). Other studies have found a dose–response-like relationship between SGA and CP in term infants (64). No such clear association has been found in preterm infants (64) but there are some indications of a similar relationship between SGA and CP in two large preterm studies (65). No data are available for true IUGR, but preliminary data from a Swedish study that used Gardosi’s customized percentiles to the full extent indicate such an association between children born at term with a history of IUGR and CP (21). The gender of the fetus also seems to influence the relationship between cerebral palsy and intrauterine growth (66). Below the 75th weight centile the prevalence of cerebral palsy for males is statistically significantly greater than that for females. At about the 90th centile the difference disappears. Male infants are according to some data up to a month less mature at term (and presumably also proportionately less mature at earlier gestations) than their female counterparts (67, 68). This maturity difference is specifically true for cerebral anatomy (lateralization (69) and myelination (70) and can be measured as differences of in utero behavioral adaptation to evoked responses (67). Such immaturity might make male brains more vulnerable to insult at a variety of stages including intrapartum stressors. There is also intriguing possibility that the optimum size at birth for males is further from their population mean weight than is true for females. The rate of cerebral palsy in males even at the 90th to 97th weight centiles is lower than for males of “normal” birth weight (25th to 75th centiles), whereas for females, the reverse is true. As male infants are significantly heavier than females, being further from optimum birth weight may arise owing to maternal constraint, a limit to intrauterine growth rate created by the limits of maternal resources which are reached earlier for the male infant than for the smaller female infant (71). Recently published review deals with associations and confusions regarding IUGR and CP (62). In these articles authors emphasize several problems that arise in the interpretation of the results from reports of the relationship between cerebral palsy and the IUGR. It has been noticed that many studies of the risk for cerebral palsy use birth weight alone unqualified by the gestational age at birth (72, 73), and because of that the observed increase in the risk for cerebral palsy associated with low birth weight has dominated the results and often been attributed to intrauterine growth retardation (74). Judgment of the relative size of infants at birth must take into account gestational age, because this age has a profound effect on the risk for cerebral palsy (75). Low birth weight infants (< 2500 g) may have elevated risks of cerebral palsy because they are (1) of optimum weight for gestation but are born too early (eg, preterm only), (2) light for gestational age but born at term (small for gestational age [SGA] only), (3) both preterm and light for gestational age, or (4) heavy for gestational age but delivered very early (one fifth of infants at greater than the 90th centile preterm weight less than 2500 g). Thus, significance of birth weight cannot be properly understood without also considering gestational duration (76).
When birth weight and gestational age data are both available, a more sophisticated account of relative size can be made using centile charts. It is important to pay attention that these centile charts are not out of date. With the average weight of healthy infants at birth increasing by up to 50 g every 10 years (77, 78), progressively fewer infants are qualifying as SGA as defined by old growth charts. The centile charts may also have insufficient adjustment for nonpathologic determinants of size for gestation, such as gender, parity, and maternal height (79).

Furthermore, the size of preterm infants should be compared with that expected of their “healthy” peers. It is now clear that infants born before 37 weeks’ gestation are not healthy in this sense but tend to be lighter (80) and slower growing (81) than fetuses of the same postconceptual age, presumably for reasons related to their preterm birth. Because conventional “neonatal” birth weight standards are based on the observed birth weights of infants born at different gestational ages, comparing the weight of preterm infants with cerebral palsy with these standards compares them with other preterm infants who themselves are more likely to be abnormally grown. To avoid this problem, the relative size of infants born beforeterm should be judged using reference standards based on the intrauterine weight-for-gestational age (“fetal” standards) rather than birth weights. Such fetal standards are derived from ultrasound-based estimates of the weights of healthy infants in utero at known gestational ages (82, 83). The standards can be tailored to allow for other important fetal characteristics, such as sex, ethnicity, and parity, as well as maternal height (84).

Authors believe that the use of gestation-matched preterm controls can make it impossible to disentangle the risk of cerebral palsy attributable to factors that are themselves associated with poor growth and preterm delivery. Also, in studies investigating the risk of cerebral palsy, neonatal weight standards were used to judge the relative size of cerebral palsy cases, often using gestation-of-delivery matched controls. (85, 86, 87, 88).

Typically, these studies reported that the risk for cerebral palsy was not elevated for very preterm SGA infants. Reason for this could be that the neonatal growth standards and the controls used were equally biased by the inclusion of an excess of abnormally light preterm infants. In addition, when fetal growth standards are used, there is a significant elevation of the risk for cerebral palsy for very preterm SGA infants in a similar pattern to that which applies at term. Intriguing question is whether cerebral palsy is a consequence, or a cause of growth deviation, or simply an associated phenomenon (62). Answer on this question can have direct impact on obstetricians. If the brain damage associated with cerebral palsy precedes growth changes, recognition of growth restriction occurs too late for preventative intervention. Furthermore, growth abnormality may be the first, albeit, crude signal that in utero pathology is occurring. This finding may indicate the need for further investigation with a view to potential in utero treatment (eg, of infections) ordelivery in optimal circumstances. If the risk for cerebral palsy is elevated as a consequence of growth deviation, underlying causes of growth abnormality may be pursued (placental compromise, gestational diabetes) or early delivery considered before fetal brain damage occurs (62).

6. NEW DATA ON CEREBRAL PALSY

The traditional concept that brain damage is caused during birth or early neonatal period has been challenged and antenatal undetectable factors are now considered as the most important etiologic factors (23, 89, 90). Cerebral palsy is an “umbrella” term for disorders of development, movements and posture, resulting in limitations of activity due to non-progressive impairment of developing brain (90). This diagnosis describes a group of disorders of development of movement and posture, causing activity limitations that are attributed to nonprogressive disturbances that occurred in the developing fetal or infant brain. The motor disorders in cerebral palsy are often accompanied by disturbances of sensation, cognition, communication, perception, and/or behavior, and/or by a seizure disorder. “Attributed to” is purposefully vague because our understanding of developmental neurobiology is evolving rapidly. “Disturbances” is used as a comprehensive term referring to events or processes that in some way interrupt damage or otherwise influence the expected pattern of brain maturation (91). These events or processes are many, with consequences varying from very conspicuous to very subtle. The worldwide prevalence ranges from 2 to 2.5 per 1000 live-births and the incidence did not change since 1951, respectively. Improvement of obstetrical and neonatal care did not result in 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. Cerebral palsy is the most common chronic motor disability of childhood. The diagnosis is retrospective and it is rarely made before the age of six months when the infant is severely affected. The specificity of the diagnosis improves as the child grows and the nature of the disability evolves (91). CP does not result from a single event but rather from a sequence of interdependent adverse events. This time frame of evolving adverse events should be taken into account when considering the possibility of CP diagnosis in infants (93). Periventricular white-matter injury is now the most common cause of brain.
injury in preterm infants and the leading cause of chronic neurological morbidity and CP. Standardized methods of clinical neurological assessment from the neonatal period onwards were developed in order to identify three grades of neurological impairment: severe, moderate and mild. The clinical identification of severely affected patients is less problematic than the identification of moderately- and mildly affected infants. Cranial ultrasound, magnetic resonance imaging, magnetic resonance spectroscopy and diffusion weighted imaging are helpful in very low birth weight premature and in term infants with encephalopathy (90).

From the pediatric experience it is well known that one should wait until the age of 6 months postnatally to be able to diagnose a severe CP. 12 months for a moderate CP and 24 months for a minor non-disabling CP. This delay for the full clinical expression of functional consequences of a brain damage depends on brain maturation. Di Pietro was right insaying that a consensus recognizing that a consensus recognizing the fact that fetal neurobehavior reflects the developing nervous system is emerging (93-95). The purposes of early diagnosis of CP could be important from the point of view of the infant, the family, and the gynecologist, who is often accused for clinical negligence. Although randomized studies confirming that the early intervention as an effective strategy for treatment of CP is not available, it should be considered as feasible. Because the etiology of CP is mostly shifted towards the prenatal period, attempts were made to diagnose neurological impairment in the perinatal period (90, 92).

One crucial question often posed to neonatologists is to determine the exact timing of brain damage, prenatal or intrapartum, in the context of neonatal encephalopathy. In this perspective, repeated neurological assessments over the first days of life allow identification of two profiles. The first, a dynamic profile, is associated with signs of CNS depression increasing within the first 3 days and then decreasing gradually with obvious improvement in alertness, motor activity, and sucking (96). This profile is typical of recent insult, most often intrapartum. The second, a static profile, is disclosed by lack of changes along repeated assessments in the first week of life. This latter profile is typical of perinatal insult that occurred in utero at least several weeks earlier and therefore, already stable at the time of birth. In addition, the identification of three signs already present at birth offers a precious clue to fetal brain damage, when observed in a cluster:

- High-arched palate (due to insufficient molding forces of anhydrous active tongue),
- Non reducible adduction of the thumb in a clenched fist (due to absence of spontaneous motor activity), and
- Cranial ridges over each suture or restricted to the squamous suture (due to severe or moderate impairment of hemispheric growth).

Using 3D US, only two of these three signs can be diagnosed in utero. As for now, it remains impossible to visualize the high-arched palate with 3D surface imaging since this technique does not permit visualization of deep structure in the oral cavity. However, the detection of the two other signs as a specific expression of brain impairment appears promising (Figure 3).

Development of Prechtl’s general movements (GM) for postnatal neurological evaluation encouraged obstetricians to implement thistechnique for fetal neurological evaluation using 2D ultrasound (23, 35). The fact that the same criteria can be used for the fetus and young infants seemed especially attractive. Development of computer and ultrasound technology enabled evaluation of fetal GM in three dimensions and in real time (97, 98). GM includes the consideration of body movements (arms, legs, neck and trunk) spreading in variable sequences with gradual beginning and end. They wax and wane in intensity, force and speed, being fluent and elegant, revealing the complexity and variability of motor activity already present even in early stage. GM has to be videotaped and then analyzed based on

![Figure 3. Neonatal signs indicating a prenatal insult (sketch pictures) and comparison with 3D-US imaging in utero. (1) High-arched palate (left) and 3D-US imaging of the entire oral cavity (right); (2) Cortical thumb in a clenched fist (left) and 3D-US imaging of the normal and abnormal hand position. (3) Cranial ridges on every suture (left) and 3D-US imaging of the normal cranial suture in utero.](image-url)
visual “Gestalt perception”, which provides an overall impression of GMs with standardized procedures (37). Subsequently, movement patterns will be described in terms of complexity, variability and fluency. GMs will finally be classified as normal-optimal, normal-suboptimal, mildly abnormal and definitely abnormal (96). While the application of GMs in postnatal life is standardized and in spite of encouraging results of fetal GMs in the last 25 years which showed that qualitative assessment of GMs is a good marker of brain dysfunction, (32) they did not shift the diagnosis of neurological impairment to the prenatal period.

The Amiel-Tison Neurological Assessment (ATNAT) relies on responses to specific maneuvers and has specific contribution in the exploration of passive and active tone according to neurological maturation (99). The clinical significance of this type of assessment was more fully understood when Sarnat (100) reviewed anatomical and physiological correlates of early neurological development. In fact, it became possible to clinically dissociate the development of upper and lower motor systems:

1. The lower system, consisting of the brainstem and cerebellum, matures early (beginning at 24 GW) in an ascending wave; its essential role is to maintain posture against gravity and flexor tone in the limbs;

2. The upper system, consisting of the cerebral hemispheres and basal ganglia, matures later (beginning at 32 GW) and rapidly for the first 2 years in a descending wave; its essential role is to control the lower system, with relaxation of the limbs and control of the antigravity forces, finally allowing erect posture, walking and fine motor skills.

This distinction became even more relevant for clinicians after pathophysiological and radiological data had shown that brain damage is mainly located in cerebral hemispheres, in the full term infant with hypoxic-ischemic en-cephalopathy or in the preterm infant with periventricular leukomalacia (PVL). The ATNAT may be used to determine the neurological status during the first days of life for full term infants or at 40 GWs (corrected age) for premature neonates. Interims of physiological correlates, it is satisfactory to cluster the different items into four subgroups according to their conceptual meaning: adequate hemispheric growth, absence of CNS depression, integrity of the upper motor control, stability of the autonomic nervous system (ANS). When result for each item is normal, it seems reasonable to conclude to CNS optimality.

Some criteria are similar in fetal and neonatal assessments: headgrowth parameters including sutures’ status, primary reflexes (restricted to sucking behavior), fingers’ movements and abduction of thumbs (shaded boxes in Table 3 (29)).

Some criteria observed in the fetus are only prerequisites for extra-uterine achievements: opening of the eyes for visual pursuit, facial expressions for social interaction. Their identification by 4D imaging, in addition to efficient and rhythmic sucking supports the absence of CNS depression.

### Optimality criteria of typical passive and active tone in the neonate cannot be elicited in the fetus: head anteflexion versus retroflexion, ventral versus dorsal incurvations in the axis, both being of the utmost importance postnatally to confirm CNS optimality. However, optimality in the fetus should be reflected in typical GMs.

Criteria aiming to check autonomic control are slightly different: typical non-stress test (NST) in the fetus and absence of reactions in the neonate.

In the presence of neurological signs, the next step is to proceed to the clinical synthesis. In the full term neonate the final categorization is based on the clustering of signs and symptoms observed within the first week of life; the non-optimal status can be graded into three categories:

- minor degree, without CNS depression
- moderate degree, with CNS depression
- severe degree, with deep CNS depression and repeated seizures

The categorization based on the different findings yielded a good inter-rater reliability with a Kappa coefficient of 0.76. As described above, the identification of “CNS depression” during fetal life is based on pre-competences requiring only the absence of specific responses.

### Table 3

<table>
<thead>
<tr>
<th>Optimality Criteria</th>
<th>ATNAT</th>
<th>Prechtl GMA</th>
<th>3D/4D-US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head circumference</td>
<td>Within normal limits</td>
<td>Same range in other growth parameters</td>
<td>Adequate hemispheric growth</td>
</tr>
<tr>
<td>Cranial sutures</td>
<td>Edge to edge, squamous included</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual pursuit</td>
<td>Easily obtainable</td>
<td>Opening of the eyes</td>
<td>Absence of CNS depression</td>
</tr>
<tr>
<td>Social interaction</td>
<td>Eager</td>
<td>Facial expressions</td>
<td></td>
</tr>
<tr>
<td>Sucking reflex</td>
<td>Efficient, rhythmic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raise to sit and reverse</td>
<td>Active flexion of the head</td>
<td>Flexion ≥ Extension</td>
<td>Optimality should be reflected in typical GMs</td>
</tr>
<tr>
<td>Passive axletone</td>
<td>Flexion ≥ Extension</td>
<td>Within normal limits</td>
<td>Integrity of the upper motor control</td>
</tr>
<tr>
<td>Passive tone in limbs</td>
<td>And symmetrical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fingers and thumbs movements</td>
<td>Independent movements of fingers</td>
<td>Active abduction of thumbs</td>
<td></td>
</tr>
<tr>
<td>Autonomic control</td>
<td>No disturbance during the assessment</td>
<td>Typical NST</td>
<td>Stability of SNA</td>
</tr>
</tbody>
</table>

*Shaded boxes indicate criteria which are similar for the fetus and the neonate

Table 3. Optimality criteria assessed in the term neonate and comparable optimality criteria observed in the fetus in the second half of pregnancy by 3D/4D sonography. (From 29)
Intrauterine Growth restriction and cerebral Palsy

Intrauterine insults, abnormalities, and impairments may have deleterious effects on fetal cerebral development. The most common types of brain injury related to perinatal brain damage are hypoxic-ischemic events, intracranial hemorrhage, porencephalic cysts, and pseudocysts, reviewed in another chapter. Non-optimal cerebral development presents an exciting opportunity to hypothesize correlations between neurocognitive disabilities and subtle diffuse brain abnormalities. However, we must refine every method of fetal assessment (fetal neurology including long term outcome measurements). Neuroradiologists know very well that the best radiologic techniques are not microscopes: many changes are below the limits of resolution of neuroimaging. Reviewing fetal and perinatal brain damage in 1998, (103) it was stressed that the group of children with normal imaging but non-optimal cerebral function presents an exciting opportunity to hypothesize correlations between neurocognitive disabilities and subtle diffuse brain abnormalities. However, we must refine every method of fetal assessment (fetal neurology included) before providing obstetricians with safe guidelines for the optimal management of fetuses at risk of neurodevelopmental disabilities. The 3D/4D-US gives hope for better future fetal management.

As far as subtle brain lesions are concerned, pathological gliosis cannot be distinguished from PVL as a diffuse lesion of white matter associated with an increase of hypertrophic astrocytes (positive withglial fibrillary acidic protein staining). When using routinely this staining, similar lesions are also detected based on the presence of reactive astrocytes in the germinal matrix; the de-population of thistransient structure that can follow a hypoxic-ischemic event may influence the latter capacity to produce neuroblasts and glial cells. In the postmigratory phase during the second half of gestation, another transient structure, the subplate, appears to be the site of selective vulnerability (104) with consequences on neocortex formation. The subplate is located between the cortical plate and the intermediate zone, reaching its maximal thickness between 22 and 36 GW. Each neuron will migrate into the subplate which plays several important roles up to term. Programmed cell death, wiring, and synaptogenesis are active processes during the second half of pregnancy, “processes that in some way interrupt, damage or otherwise influence the expected pattern of brain maturation”.71

Those damages can occur in utero but they probably occur as wellin postnatal life in many extremely low birth weight (ELBW) infants. It is known that in this risk group the incidence of PVL is not higher than in the LBW group. However, we are aware of the high incidence of learning disabilities in the ELBW group (nearly half of them when tested from 7 to 9 years). It is obviously tempting to correlate those developmental sequelae to those subtle damages, as a result of earlycerebral disorganization without macroscopic tissue destruction, and without detectable imaging.

Finally, it appears that when we consider not only CP, the tip of the iceberg, but the full spectrum of motor disorders, the moderate and mild clinical aspects are much more frequent than the severe ones. It is probably the same proportion for the pathologist between the clasticforms of brain damage and the more subtle and diffuses tissue impairment. However, we cannot equate clastic damage-positive imaging and CP on the one hand, and diffuse damage and negative imaging with milder disabilities on the other hand. Those categories overlap, i.e., some cases of the CP are not associated with clastic imaging and some cases with subtle motor disability (non-disabling CP) are associated with, for instance, obvious scars of PVL. In conclusion, clinicopathological correlations are established statistically but have to be applied with caution for

the left cerebral hemisphere may look fine when he sits independently at 7 months or walks independently at 18 months. However, at age 7 years with a confirmed diagnosis of hemiplegic CP, severe motor disorders are accompanied by disturbances of sensation, cognition, perception, behavior and a seizure disorder. As a conclusion, it is wise to check down the road: for each specific type of fetal brain damage, appropriate decisions for a conservative management have to rely on series including long term outcome measurements.

An atlas on fetal CNS diseases recently reviewed fetal brain imaging; one chapter covers any visible congenital brain anomalies (101) while acquired brain abnormalities in utero including destructive lesions due to hypoxic-ischemic events, intracranial hemorrhage, porencephalic cysts and pseudocysts, are reviewed in another chapter (102). The probability outcome may be estimated according to fetal age at the time of diagnosis, size and location of clastic lesions or structural abnormalities as well as the degree of severity of functional consequences evaluated by 4D-US. How to use that information still remains tigious in many cases, depending not only on ethical positions (personal or national) but also expectations concerning the degree of cerebral plasticity at this earlystage. We understand morphologists and neurosurgeons that often refer to a few personal cases with a favorable motor outcome despite very destructive brain lesions: they optimistically conclude that morphology does not always correlate with neurodevelopmental outcome. On the contrary, pediatricians and neuropsychologists involved in long term follow-up studies certainly are less optimistic. For example, an infant born with a massive destruction of the whole Sylvian artery territory in.

(opening of the eyes, variety of facial expressions), primary reflexes (rhythmic bursts in the sucking pattern) and quality of GMs. The addition of cranial signs (such as insufficient head growth and overlapping sutures) to neurological signs could be a valuable complement. Moreover, the identification of dynamic and static patterns of the symptoms may be as helpful to date the insult as it is postnatally: the more stable the signs, the more precocious the insult. Seizures are known to occur in utero, abnormally rhythmic movements having been occasionally perceived and reported by mothers. However, it is unlikely that such a brief and rare event should be seen with 4D-US.
each individual case. The main obstacle to early prediction of CP based on a functional observation of the fetus such as observation by 3D/4D-US is due to the ‘precompetent’ stage of most of the motor abilities observed in utero. In other words, can we predict the presence or absence of hemispheric brain damage, based on the observation of motor and reflex activity under the control of lower structures? The clinician is able to follow the switch in neural circuitry observed for each motor acquisition according to a specific chronology. As most of the hypoxic-ischemic damages of minor and moderate degrees are located in the cerebral hemispheres, it seems unwise to expect reassurance about the integrity of upper structures based on precompetent functional stages. Nevertheless, it remains important to test the integrity of the lower system as a prerequisite for a favourable outcome. This dilemma is not specific to neuromotor function. For example, fetal habituation which has attracted a lot of attention as a potential means of assessing fetal neural integrity may just be a prerequisite depending on the lower system (105). More longterm data are necessary to establish its predictive value for later development.

7. NEW SCORING SYSTEM FOR FETAL NEUROBEHAVIOR ASSESSED BY 3D AND 4D SONOGRAPHY

One of the most promising improvements in the unknown field of prenatal behavior has been the new 3D/4D-Ultrasound technology. Its advance has been completed in giving visualizations in almost real-time and production of standards for different movement patterns to appear and develop. The 4D study of fetal behavior provided us with a great possibility of understanding the hidden function of the developmental pathway of the fetal CNS and the potentialities of originazing a neurological investigation in utero. By 4D technology we might be able to visualize an intrauterine neurological condition that would enable to identify which fetus is at risk and which is not. Existence of motoric competence in the newborn, even preterm infants is assumed to have its origins in prenatal life. Behavioral perinatology assessed by 4D sonography should be an interdisciplinary area of research involving concepts and conducting studies of the dynamic interplay between behavioral processes in fetal, neonatal, and infant life. The ultimate clinical application of fetal neurobehavioral assessment will be to identify functional characteristics of the fetus that predict a range of subsequent developmental dysfunction. Establishing this link will require demonstration of positive and negative predictability to outcomes significantly beyond the immediate perinatal period. After standardization of a valid reference ranges of movements appropriate for the gestational age, attempts have been made to produce a new scoring system for fetal neurobehavior based on prenatal assessment by 3D/4D sonography (106, 111-114). That preliminary work may help in detecting fetal brain and neurodevelopmental alterations due to in utero brain impairment that is inaccessible by any other method.

In the recent study, the Zagreb group published a new scoring system for fetal neurobehavior based on prenatal assessment by 3D/4D sonography (106). That scoring system is a combination of some parameters from fetal GM assessment and parameters from postnatal ATNAT which can be prenatally easily visualized by 4D-US (107, 108). The parameters were chosen based on a developmental approach to the neurological assessment and on the theory of central pattern generator GM emergence. They were the product of multicentric studies conducted during several years which resulted with the most significant parameters for the assessment of fetal neurological development (Table 4). (42, 109, 110).

The authors developed a three-point scale for isolated head anteflexion, isolated hand, leg, hand to face and finger movements, while for the assessment of cranial sutures, isolated eye blinking, facial alterations and mouth opening two-point scale was applied. The distinction between scores 0 and 2 is evident, whereas uncertainty may exist with regard to the assignment of a score of 1, the latter indicating an abnormal result of moderate degree. The prescidescription of the moderate abnormal performance is included for each item in the record form. Interpretation of total score is given in Table 5.

To produce the new scoring test the Zagreb group identified severely brain damaged infants and those with optimal neurological findings by comparing fetal with neonatal findings. In the group of 100 low-risk pregnancies they retrospectively and prospectively applied the new scoring system. After delivery, postnatal neurological assessment (ATNAT) was performed (95) and all neonates assessed as normal reached a score between 14 and 20, which was assumed to be a score of optimal neurological development. New scoring system was applied in the group of 120 high risk pregnancies in which, based on postnatal neurological findings, three subgroups of newborns were found: normal, mildly or moderately abnormal and abnormal. Based on this, a neurological scoring system has been proposed. All normal fetuses reached a score in the range from 14 to 20. Ten fetuses who were postnatally described as mildly or moderately abnormal achieved prenatal score of 5 to 13, while another ten fetuses postnatally assigned as neurologically abnormal had a prenatal score from 0 to 5. Among this group four hadalobar holoprosencephaly, one had severe hypotensive hydrocephaly, one had tanatophoric dysplasia and four fetuses had multiple malformations.

Based on several years of research that group of authors has proposed a new test for antenatal application. There is a similarity between neonatal optimal-
Intrauterine Growth Restriction and Cerebral Palsy

In this study 7 fetuses had abnormal KANET scores, and 25 fetuses were borderline, which gives all together 32 fetuses at neurological risk. Of 7 fetuses with abnormal KANET, postnatal neurological assessment by Amiel Tison’s method (ATNAT) revealed 3 newborns (arthrogryposis, vermis aplasia and neonate of the mother with the previous child with CP) out of 7 fetuses to be abnormal, while 4 were considered normal (ventriculomegaly, preeclampsia, thrombophilia, oligohydramnios). Out of 25 borderline KANET fetuses there were 22 borderline newborns by ATNAT, while 3 were normal (ventriculomegaly, syndrome of intraamniotic infection, mother’s thrombocytopenia). 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 intraamniotic infection, IUGR, trisomy 21, thrombocytopenia, thrombophilia, preeclampsia, achoandroplasia, oligohydramnios. Out of 3 abnormal neonates after ATNAT assessment, 2 had definitely abnormal Prechtl’s premature general movements (arthrogryposis and vermis aplasia), and additional 6 were considered abnormal (neonate of the mother with the previous child with CP, Dandy Walker syndrome, hydrocephaly, trisomy 21, ventriculomegaly, non immune hydrops). Rest of 24 children had normal optimal or normal suboptimal GMs.

The three very illustrative cases with abnormal KANET scoring were arthrogryposis, vermis aplasia, and fetus whose previous sibling had verified CP. The fetuses in these three cases had especially reduced facial movements the faces were like mask during repeated scans. Fetuses with vermis aplasia and arthrogryposis had normal cranial sutures but the isolated head flexion was small in range for both cases. Isolated hand movements, hand to face and leg move-

### Table 4. Antenatal Neurological Screening Test (KANET)

<table>
<thead>
<tr>
<th>Sign</th>
<th>Score 0 Score</th>
<th>Score 1 Score</th>
<th>Score 2 Score</th>
<th>Sign Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated head anteflexion</td>
<td>Abrupt</td>
<td>Variable in full range, many alternation (&gt; 3 times of movements)</td>
<td>Variable in full range, many alternation (&gt; 3 times of movements)</td>
<td></td>
</tr>
<tr>
<td>Cranial sutures and head circumference</td>
<td>Overlapping of cranial sutures head circumference below or above the normal limit (-2SD) according to GA</td>
<td>Normal cranial sutures normal head circumference</td>
<td>Normal cranial sutures normal head circumference</td>
<td></td>
</tr>
<tr>
<td>Mouth opening/yawning or mouthing</td>
<td>Not fluent(1 – 3 times of movement)</td>
<td>Not fluent(1 – 3 times of movement)</td>
<td>Not fluent(1 – 3 times of movement)</td>
<td></td>
</tr>
<tr>
<td>Isolated hand movement</td>
<td>Cramped</td>
<td>Variable and complex</td>
<td>Variable and complex</td>
<td></td>
</tr>
<tr>
<td>Isolated leg movement</td>
<td>Cramped</td>
<td>Variable and complex</td>
<td>Variable and complex</td>
<td></td>
</tr>
<tr>
<td>Hand to face movements</td>
<td>Abrupt</td>
<td>Variable in full range, many alternation (&gt; 5 times of movements)</td>
<td>Variable in full range, many alternation (&gt; 5 times of movements)</td>
<td></td>
</tr>
<tr>
<td>Fingers movements</td>
<td>Unilateral bilateral clenched fist, (neurological thumb)</td>
<td>Smooth and complex, variable finger movements</td>
<td>Smooth and complex, variable finger movements</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gestalt perception of GMs</th>
<th>Definitely abnormal</th>
<th>Borderline</th>
<th>Normal</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 5. Allocation of fetuses according to Antenatal Neurological Screening Test**

<table>
<thead>
<tr>
<th>TOTAL SCORE</th>
<th>INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>Abnormal</td>
</tr>
<tr>
<td>6-13</td>
<td>Borderline</td>
</tr>
<tr>
<td>14-20</td>
<td>Normal</td>
</tr>
</tbody>
</table>

The potential of the test was investigated at four university departments. The objective of this multricentric study (ii) was to apply the new antenatal scoring system, named Kurjak antenatal neurodevelopmental test (KANET) to the fetuses from high risk pregnancies for neurological disorders and to verify the results of the test by two neonatal neurological tests: Amiel-Tison Neurological Assessment at Term (ATNAT) and general movements test by Prechtl. 288 pregnant women meeting the inclusion criteria given in the Table 6 (111) were found eligible to be included in the study.
ments were poor in repertoire for all three cases. The finger movements were cramped and invariable in all three cases. The Gestalt perception of General movements was abnormal in all three cases. Results of this study show that the new test might be useful in standardization of neurbehavioural assessments. Furthermore there is a potential for antenatal detection of serious neurological problems. At this stage test easily separates serious structural anomalies associated with brain impairment (arthrogyrosis, vermian aplasia, and anencephaly). Recent study showed a significant difference for 8 out of 10 parameters of KANET: isolated anteflection of the head, eye blinking, facial expressions (grimacing, tongue expulsion), mouth movements (mouthing, jawing, swallowing), isolated hand movement, hand to face movement, fist and finger movements, and GMs. Authors have also confirmed statistically significant, moderate correlation of KA-
NET and ATNAT tests. In practical sense, it means that the neu-
ropediatrician who examined the newborns with ATNAT test con-
firmed the results of KANET.

This is work in progress and four collaborating centers are continuing investigation. In some of the centers (Doha, Zagreb) preliminary results are already obtained after one year of life. The new test might be a promising tool for the assessment of integrity of young central nervous system. However, the test requires further multycentric studies before recommended for wider clinical practice. We believe that the concept of KANET can be simplified and the time of the examination shortened. This could be achieved by grouping several similar parameters in to main categories and by certain changes in the scoring system. In the mean time the potential of antenatal scoring system shouldn’t be neither over-
estimated nor underestimated.

8. CONCLUSION

Despite medical reports from 100 years ago and 25 years of sys-
tematic research initiated by Pre-
chtl and colleagues, the study of pre-natal behaviour is still in its infancy. One of the most promising advances in the field of ultra-
sonography has been the new 4D-US technology. Its advance has been completed in giving visualiza-
tions in almost realtime. The availability of new diagnostic data has in an extraordinary way raised our knowledge about intrauterine
life, substantially modifying some earlier interpretations. The 4D study of fetal behavior provided us with a great possibility of understanding the hidden function of the developmental pathway of the fetal CNS and the potentiali-
ties of originating a neurological investigation in utero. Now, by 4D technology, we might be able to visualize an intrauterine neurological condition that would enable to identify which fetus is at risk and which is not. Existence of mo-
toric competence in the newborn, even preterm infants is assumed to have its origins in prenatal life. Behavioral perinatology assessed by 4D sonography should be an interdisciplinary area of research involving concepts and conducting studies of the dynamic inter-
play between behavioral processes in fetal, neonatal, and infant life. The ultimate clinical application of fetal neurobehavioral assessment will be to identify functional characteristics of the fetus that predict a range of subsequent de-
velopmental dysfunction. Establishing this link will require demonstration of positive and negative predictability of outcomes signi-
ficantly beyond the immediate perinatal period. Afterstandard-
ization of valid reference ranges of movements appropriate for the gestational age, attempts have been made to produce a newscoring system for fetal neurobehavior based on prenatal assessment by 3D/4D sonography. That preliminary work may help in detect-
ing fetal brain and neurodevelopmental alterations due to in utero brain impairment that is inaccessible by any other method. It would be advisable to investigate the usefulness of new KANET test to identify the endangered fetuses from specific high risk pregnancies at neurological risk, like pregnancies complicated with IUGR.

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