Intrauterine Growth Restriction and Cerebral Palsy

Asim Kurjak[1,2], Maja Predojevic[3], Milan Stanojevic4, Aida Salihagic-Kadic[3,5], Berivoj Miskovic[1], Ahmed Badreldeen[2], Amira Talic[6], Sanja Zaputovic[1], Ulrich Honemeyer[7]

Department of Obstetrics and Gynecology, University Hospital "Sveti Duh", Medical School, University of Zagreb, Zagreb, Croatia[1]

Feto Maternal Medicine Unit, Women's Hospital, Hamad Medical Corporation, Doha, Qatar[2]

Department of Physiology, Medical School, University of Zagreb, Zagreb, Croatia[3]

Division of Neonatology, Department of Obstetrics and Gynecology, Clinical Hospital "Sv. Duh", Zagreb, Croatia[4]

Croatian Institute for Brain Research, Medical School, University of Zagreb, Zagreb, Croatia[5]

University of Medical Sciences and Technology, Khartoum, Sudan[6]

Welcare Hospital, Dubai, UAE[7]

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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 reaserch 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 gestationalage. The term IUGR should be used only in regard to thefetus, whereas SGA should be used mainly in the newborn(but it can be estimated from sonographic measurementsof the fetus) (2). IUGR is ideally detected by adiminished growth velocity of the fetus on serial ultrasonographicscans (6). In this way, the function ofgrowth becomes the object of interest instead of theresult (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 mention, 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 geneticall 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 a (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 admittances 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 ofunfavourable neurodevelopmental outcomes. They are fairly reliablein predicting very poor outcomes as well as optimal outcomes.However, within these two extremes, the prediction still re-

mains achallenge (22). Furthermore, there is a growing pool of evidence that many neurological disordersoriginate from intrauterine rather than perinatal or postnatal period.In addition, clinical and epidemiological studies have shown that evencerebral palsy (CP) most frequently results from prenatal rather thanperinatal or postnatal causes (23). As the neuromotor system is the first to mature and cranialexpansion passively follows hemispheric growth, neurologicalassessment should be able to produce early markers to predict lateroutcomes based on neuromotor and cranial findings. For many years,obstetricians have worked toward the same objective as neonatologists by monitoring fetalwell-being during pregnancy. They rely on technical advances, namelyultrasonography (US) which has lead to the following statement: "Fetalbehaviour can be defined as fetal activities observed or recorded withultrasound equipment" (24).The advent of US has led to a kind of revolution. For more than 40 years, ultrasound has been extensively used in medicalimaging, providing help for the diagnosis and staging of numerousdiseases of different organs and systems of human body. Thedevelopment of real time two-dimensional (2D) ultrasound has enabledthe direct visualization of fetal anatomy and activity in utero. Analysisof the dynamics of fetal behaviour in comparison with morphologicalstudies has led to the conclusion that fetal behavioural patterns directlyreflect developmental and maturational processes of fetal centralnervous system. Therefore, it was suggested that the assessment of fetalbehavior and developmental processes in different periods of gestationmay make possible the distinction between normal and abnormal braindevelopment, as well as early diagnosis of various structural orfunctional abnormalities (25). However, 2D ultrasound was consideredsomewhat subjective method because information needs observerinterpretation. The latest development of three-dimensional (3D) andfour dimensional (4D) sonography that overcame some of the limitationsof 2D methods enable precise study of fetal and even embryonic activityand behavior. Contrary to the 3D ultrasound which freezes the image of an objectand therefore does not provide information on movements, 4D enablesthe opportunity of simultaneous visualization of the movements of thehead, body, and all four limbs and extremities in three dimensions, in areal-time mode. 4D ultrasound or real-time 3D ultrasound makes it straightforwardto comprehend some morphological dynamics, such as yawning,sucking, smiling, crying and eye blinking. This offers a practical meansfor assessment of neurophysiologic development, as well as for detectionof anatomical pathology (26, 27). New diagnostic tool additionally providesa possibility of spatial observation of fetal face, which was not provided by 2D sonography (28). 4D therefore allows the appearanceand duration most of the each facial movement and expression to bedetermined and measured (Figure 1, 2).

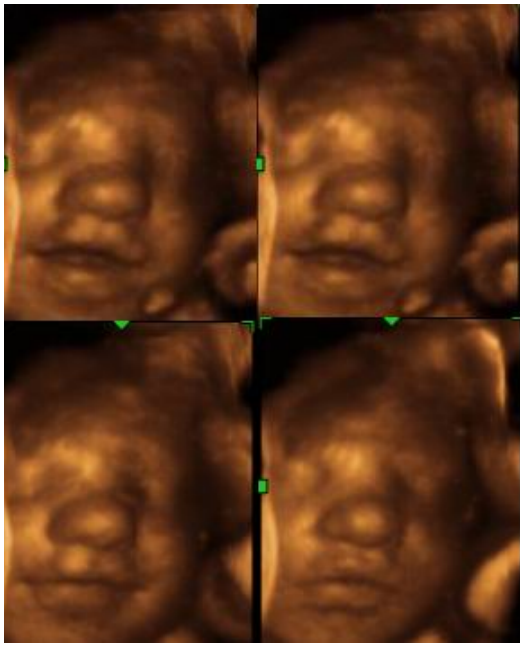
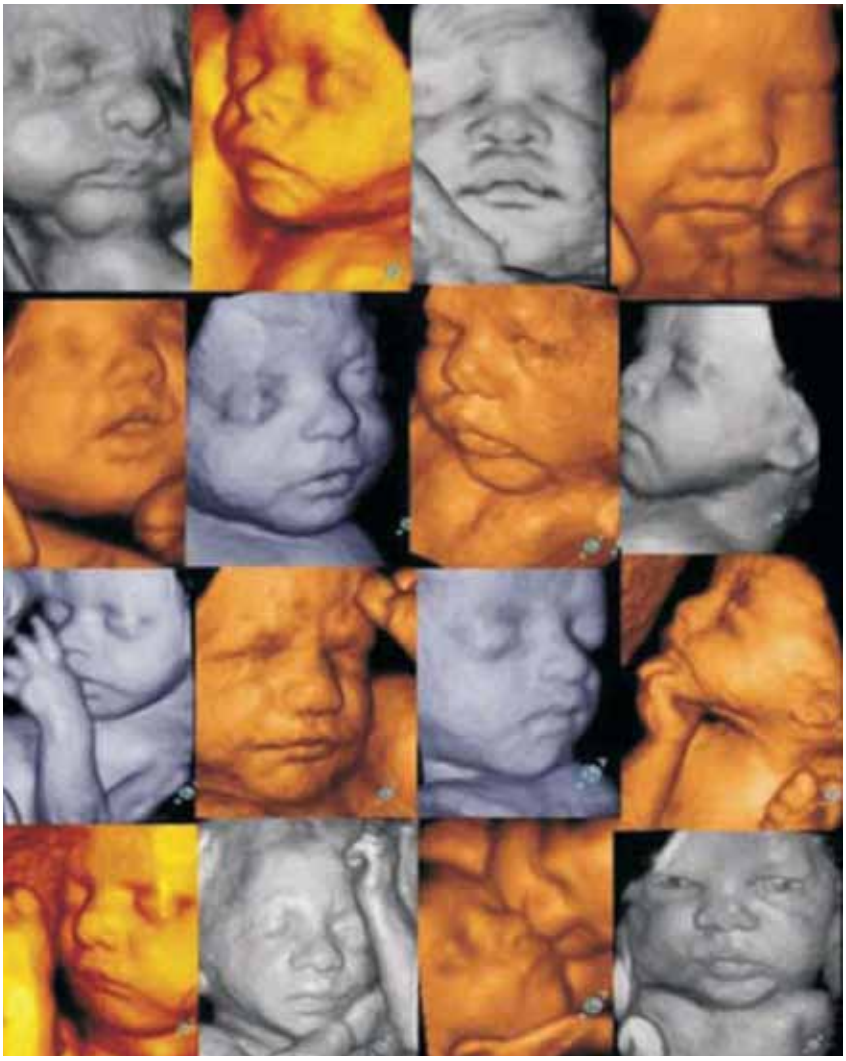


Figure 1. A sequence of images of the fetus in the 3rd trimester recorded by 3D/4D sonography, exhibiting smiling movements.

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

The visualizationof fetal activity *in utero* by 4D ultrasound could allow distinctionbetween normal and abnormal behavioral patterns which might makepossible the early recognition of fetal brain impairment (30, 31). As it is not yet possible to assess functionaldevelopment of the CNS directly, investigators have started to analyzefetal behavior as a measure of neurological maturation icluding-properties of fetal hemodynamics and the muscular system, as well (32).US technique allowed the investigation of spontaneous fetal motoractivity *in utero*. Since fetalbody movements give important information about the condition ofthe fetus, their quantitative as well as qualitative aspects were analyzed. For many years the interest of obstetricians was focused on thequantity of fetal movements which was considered as an indicator offetal well-being. Later studies on the subject have shown that movementcounts are poor indicator of brain damage, mainly because the great intra- and inter-individually differences and the large overlap betweennormal and abnormal, which makes this method clinically useless. Onthe other hand, changes in the elegance and fluency, as well as thevariability and fluctuation of intensity and speed of motor performanceswere shown to be prominent in the sick preterm infants. It becameevident that the qualitative changes in motor patterns of both the fetusand neonate precede quantitative changes when the integrity of thenervous system is impaired. It must be admitted that it is more difficultto objectify complex qualitative changes than

it is simply to countcertain events when they occur, but the Gestalt-perception is excellentmethod for dealing with such phenomenon. Important step is videorecording of movements of sufficient length to make a selection ofseveral 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, andare fluent and wax and wane in their intensity. GMs are selected forjudgement only if they last for 20 seconds or longer. If the GMs aremonotonous, have less complexity and are repetitive in pattern, theyare judged as abnormal and as being of "poor repertoire". Otherabnormal patterns are the "cramped-synchronised" type, when themovements are occurring en block and generalized muscle contractionand relaxation appear almost simultaneously, or the movements mayoccur in a jerky and exaggerated manner and in chaotic order. If themovements last very shortly and hence, they are difficult to be judgedand then we speek of "hypokinesis". Several studies employing thisnew assessment have been carried out and they showed that the earlynormal or abnormal findings of the GM quality are highly predictivefor later outcome (33, 34).Assessment of GMs is based on the concept of ontogenetic adaptationcorresponding to the development of human organism, which is duringeach developmental stage adapted to the internal and externalrequirements. Prechtl stated that spontaneous motility, as the expressionof spontaneous neural activity, is a marker of brain proper or disturbedfunction (23, 35). The observation of the unstimulated fetus or infant whichis the result of spontaneous behavior without sensory stimulation isthe best method to assess its central nervous system capacity. Allendogenously generated movement patterns from an unstimulatedcentral nervous system could be observed as early as from the 7 to 8 weeks of postmenstrual age, with a reach repertoire of movementsdeveloping within the next two or three weeks, continuing to be presentfor 5 to 6 months postnatally.The identification of "CNS depression" during fetal life is based onpre-competences (opening of the eyes, variety of facial expressions),primary reflexes (rhythmical bursts in the sucking pattern) and qualityof GMs (34, 36, 37). The addition of cranial signs (such as insufficient headgrowth and overlapping sutures) to neurological signs could be avaluable complement (34, 36). Moreover, the identification of dynamic andstatic patterns of the symptoms may be as helpful to date the insult as itis postnatally: the more stable the signs, the more precise is the timingof 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 examineesshould be followed till the age of two years, when their categorizationto disabling or non- disabling CP can be possible, based on clinicalneurological findings and presence or absence of the ability to walk.Obstetricians would have a great benefit if it were possible to assessthe condition of the fetal nervous system especially due to the fact thatin many cases obstetricians are held responsible for brain damage inneonates, regardless of a growing pool of evidence that most of suchdamages are consequences of prenatal complications. Even after thefetal brain anatomy can be visualized by ultrasound and thedevelopment of the fetal brain is well understood, not much is known-



Figere 2. 3D surface rendering mode of the different fetal facial expressions in the third trimester. This ultrasound mode enebles the investigation of behavioural fetal facial expression.

Author	Year	Main findings
Kuno et al	2001	Provided a novel means for evaluation of fetal behavior in the early second trimester of pregnancy.
Kurjak et al	2002	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.
Kurjak et al	2003	Enhanced determination of exact direction of the fetal hand and improved assessment of complex fetal facial activity and expression.
Andonotopo et al	2004	Better assessment of general movements. A review.
Kurjak et al	2004	Enhanced assessment of fetal behavior, and proved continuation from fetal to neonatal behavior.
Hata et al	2005	Provided novel means for evaluation of fetal movement, particularly fetal facial expression, in the second and third trimesters.
Andonotopo et al	2005	Allowed early diagnosis of a functionally affected anencephalic fetus.
Kurjak et al	2005	Enhanced depiction of different facial expressions and movements, which might represent fetal awareness.
Andonotopo et al	2005	Both 2D and 4D methods are required for the assessment of early fetal motor development and motor behavior.
Kurjak et al	2005	Rewiewed antenatal development of fetal behavioural patterns
Kurjak et al	2005	Both structural and functional early human development are illustrated. A review
Pooh et al	2005	Enhanced assessment on details of fetal hand or finger positioning and movement in early pregnancy in vivo
Salihagic et al	2005	Reviewed a significant advance in studying fetal behavioral patterns and understanding structural and functional development of fetal CNS.
Kurjak et al	2006	First paper on longitudinal assessment of normal neurobehavioral development by 4D-US.
Yigiter et al	2006	Prospective randomized study on fetal facial expressions and fetal movement patterns in all three trimesters.
Yan et al	2006	4D analysis of fetal facial expression early in the third trimester.
Morokuma et al	2007	First simplified ultrasound screening for fetal brain function based on behavioral patterns.
Kurjak et al	2007	New scoring system for fetal neurobehavior assessd by 3D and 4D-US.

Table 1. Aditional findings of fetal behavior by 4D ultrasound in published reports. (From 29)

about the functional development of the fetal CNS. In other words, thefetal CNS is not accessible. It is possible only to ascertain the output ofthe CNS, i.e. 'fetal behavior'. Observation of fetal behavior provides adirect assessment of the most important human organ. It is possible tolook closely at the functioning of the CNS and the brain. Prenatal motilityis considered to reflect the developing nervous system but also involvesfunctional and maturational properties of fetal hemodynamic and themuscular systems (38). Prechtl and his coworkers (39) have exploredspontaneous motility during human development. They introduced theconcept of ontogenic adaptation, meaning that during eachdevelopmental stage, the functional organization has to take intoaccount internal and external requirements. Any fetal brain damagewill interfere with endogenous motor activity. Therefore, spontaneousmovements, as an expression of neural activity, could be used as amarker for fetal brain status. Consequently, the observation of the unstimulated fetus or infant should contribute significantly to theassessment of central nervous system (CNS) function. Even afterdelivery, behavioral patterns frequently provide the most usefulindicators of brain function in spite of having extending acces toneurological, physiological and pharmacological measures (38). Thisremarkable continuity of endogenously generated activity from prenatalto postnatal life may allow identifying those fetuses and infants withemerging neurological impairment. During the nine months of gestation, the repertoire of fetal activitiesconstantly expands, correlating precisely with structural developmentof the CNS (40). Major developmental events, such as the establishmentof neural connections in the different regions of the brain, are accompaniedby the occurrence of new patterns of fetal activity or with thetransformation of the existing patterns. The organization of behavioralstates during the final weeks of pregnancy shows that the connectionbetween cerebral cortex and periphery is established, and that thecerebral cortex takes control over fetal activity. This also indicates theability of the fetus to perceive and process external signals. Furthermore,the latest results indicate that even higher brain functions, such aslearning, develop in utero during the last weeks of gestation (40).The major problem with the study of fetal behavior is that it is verytime consuming and not enough functional for routine clinical practice.The question of subjectivity should be overcome using recording ofinformation. Nevertheless, there is no other possibility of assessing thefunction of the CNS in utero, and this is needed for understanding ofthe hidden information in the neurodevelopmental pathways of thefetal CNS. Only if normal behavior is fairly understood, is it possible toidentify and to perceive abnormal behavior before birth (28, 41). First reports on fetal behavior obviously suggested that these studiesshould be standardized as much as possible. An objective analysis withstrict application techniques and the use of valid reference rangesappropriate for the gestational age are essential (32). Without suchstandardization, comparisons with former or future measurements ofpatients and comparable studies cannot be made. In order to achivethis goal the Zagreb group published the first study which describedthe 4D sonographic techniques used for obtaining longitudinal standardparameters 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 withgestational age. Those parameters have been followed longitudinallythrough all trimesters and showed increasing fre-

quency of fetalmovements during the first trimester. A tendency towards decreasedfrequency of facial expressions and movement patterns with increasinggestational age from second to third trimesters has been confirmed (42).Despite the longstanding conclusion that it is possible to make validconclusion about brain function from observed, no generalized antenatalbehavior screening has been developed to identify fetuses that mayhave central nervous system defects. Recent study from Morokumatried to produce screening test that would be less time consuming andin that way cost effective as compared to their previous study (43). Theydevised a brief ultrasound examination to distinguish fetuses withcompromised central nervous system function from the generalpopulation and evaluated it with their study (44). The study designcompared findings on five behavioral patterns obtained byretrospectively reviewing the ultrasound examinations of 5 fetuses thathad abnormal behavior with prospectively obtained findings of 29normal fetuses. Median time for brief examination criteria was 50minutes (range 30 to 60 minutes) with the only case undetectable bythis brief ultrasound examination had an eye-movement periodsignificantly longer than the normal upper limit.Improvements in technology and procedures that provide directaccess to the fetus in utero are generating the impetus for prenataldevelopmental research to move beyond the simple documentation thatbehaviour abnormalities during pregnancy can produce effects that areevident in their offspring after birth. Rather, we see a growing need fordevelopmental researchers to focus attention on how prenatal eventsaffect the fetus, its behavior, and its relationship with environmentalconditions in utero. Investigation of behavioral potentials in the fetuswill promote understanding of the mechanisms of normal and abnormaldevelopment that lead to predictable behavioral outcomes after birth.In other words, behavioral study of the fetus will be necessary tounderstand the origins of motor and sensory capabilities of infants andthe mechanisms of altered developmental outcomes (36).Awareness of changing risk, and the potential for significantneurodevelopmental problem, is an underlying principle of perinatalmedicine. Unfortunate neurological outcomes often result from a delay in recognizing or responding to CNS developing risk. This factor maynecessitate the timely referral of individuals to an appropriately staffedfacility. The timing of referral can be critical but, there are obviousdifficulties which may result in the decision to refer being consideredunnecessary, or on the other hand, too late.

4. FETAL BEHAVIOR IN PREGNANCIES COMPLICATED BYINTRAUTERINE GROWTH RESTRICTION

Studies dealing with fetal behavior in IUGR pregnancies are presentedin Table 2 (45). One of the first studies on the impact of growth restrictionon the fetal behavior focused on fetal breathing and on the course ofbehavioral state (46). To achieve that goal Van Vliet and his group usedrealtime ultrasound scanners to detect fetal eye, body, and breathingmovements, and the fetal heart rate of 12 growth-retarded fetusesbetween 36 and 40 weeks of gestation. The mean incidence of fetalbreathing was greater during periods of fetal activity (body and eyemovements present, greater heart rate variability) than during quiescence (body and eye movements absent, narrowed heart ratevariability) at all gestational ages studied in both low-risk and growth retardedfetuses. During periods when one of the state variables was inits active condition while the other two were quiet, or the reverse, theincidence of fetal breathing was intermediate between those found whenall three state variables were in agreement. After behavioral states haddeveloped, at 38 and 40 weeks, the mean incidence of fetal breathing inthe low-risk fetuses was greater during active states than during thequiet state. There was no apparent increase in the degree of linkagebetween fetal breathing and other expressions of fetal activity after theemergence of behavioral states (46). In another study by the same groupbehavioral state observations were carried out on 12 fetuses whichsubsequently had birth weights below the 10th percentile (47). Theirgestational ages at the time of study ranged from 32 to 40 weeks. Realtimeultrasound scanning was used to detect fetal body and eyemovements, and the fetal heart rate was continuously recorded using aclinical fetal monitor. The appearance of states seemed to be delayed inthe growth-restricted fetuses since states were present in only three ofeight growth-restricted fetuses studied at 40

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

Table 2. Aditional 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 theoccurrence of defined combinations of parameters of the state variablesat earlier ages. The results from this study showed that the growth restrictedfetuses have impaired quality and quantity of somatic motilityin comparison to low risk fetuses of equivalent gestational age. Theseobservations suggest that some aspects of central nervous systemfunction are disturbed in growth-retarded fetuses, even in the absenceof fetal distress.19Since asymmetrical intrauterine growth restriction occurs earlier thansymmetrical or combined one it was important to study the fetalbehaviour in the group of fetuses that develope growth restriction inearlier gestational age. For that purpose the behavior of 15 asymmetricalintrauterine growth restricted fetuses was compared to that of a controlgroup of healthy fetuses by simultaneous cardiotocographic andultrasonographic examinations (48). Behavioural states analysis wascarried out according to Nijhuis et al. (49) and fetal movements wereautomatically 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 betweenhealthy and IUGR fetuses. On the other hand quantitative differenceswere 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 statevariable when compared to the control group fetuses. These findings,therefore suggest the existence of quantitative differences in fetalbehaviour in asymmetrical IUGR fetuses when compared to healthyfetuses (48). To see wether these differences were caused by thecompromised vascularization the degree of vascular peripheralresistance was evaluated by means of pulsed doppler ultrasonicequipment in the group of asymmetrical growth restricted fetuses andin control group (50). All fetuses underwent simultaneous cardiotocographicand echographic examinations for two consecutive hours at36-38 weeks of gestation. The distribution of gross fetal bodymovements, fetal breathing movements and fetal eye movements wasanalysed during the different fetal heart rate patterns. Furthermore,the incidence and organization of fetal behavioural states wasinvestigated. Growth restricted fetuses were divided into two groupson the basis of the presence or absence of end diastolic flow in the fetal thoracic descending aorta. The results were in accordance with previousfindings that growth restricted fetuses showed a delay in the integrationof behavioural patterns and a lower coincidence of behavioural states.These findings are particularly evident in the fetuses with a severeincrease of peripheral vascular resistance (absence of end diastolic flowin descending aorta) suggesting that a delay in central nervous systemdevelopment is present in asymmetrical growth retarded fetuses andthat there is a possible relationship of this delay to the degree ofperipheral vascular resistance.Since general movements are considered to be important forprediction of fetal neurobehavior next step was to study the effect ofsevere intrauterine growth restriction on its quality (51). The study wasperformed longitudinally in 17 human fetuses and fetal movementswere recorded by means of weekly 1 h ultrasound and video registrations,following by neurological examinations after birth. No clear effect ofuncomplicated intrauterine growth restriction could be detected on thequality of general movements, but the quality was disturbed. Generalmovements became slow and small in amplitude in cases where therewas a reduction in the amount of amniotic fluid. Parallel to the onset ofabnormal fetal heart rate patterns, general movements became poor inrepertoire, while they were hardly discernible after further deteriorationof the fetal condition. With the exception of 3 infants with cerebralhaemorrhages, the quality of general movements observed just beforeand after birth was identical. In these infants, the quality of generalmovements as well as the results of the standardized neurologicalexamination tended to normalize at 3 months and 1 year, respectively.This study showed that in contrast to prenatal period uncomplicatedIUGR had no marked effect on the quality of general movements or onthe results of the neurological examination at the age of 1 year (51). Inanother study by the same group 17 fetuses with intrauterine growthrestriction (IUGR), the quantity of general movements and fetal breathingmovements were studied both cross-sectionally and longitudinally (52). InIUGR fetuses, cross-sectional comparisons were made between thequantity of fetal movements and the fetal clinical condition and thequality of general movements. In addition, the quantity of fetalmovements in IUGR was compared with that in uncomplicatedpregnancies and in pregnancies complicated by premature rupture ofthe amniotic membranes. In IUGR, the quantity of general movementsdeclined from 25 weeks gestation onwards, whereas the quantity of fetalbreathing movements increased. Longitudinal assessment of theseparameters was obtained in four cases and showed a decline of generalmovements. No relationship between prenatal longitudinal data andneonatal outcome could be observed. The quantity of general movementsas well as that of breathing movements was low in IUGR group withabnormal fetal heart rate patterns compared to group with normalparameters. In group with reduced amount of amniotic fluid only thequantity of

breathing movements and not of general movements waslow. A similar pattern was found in the relation with the quality ofgeneral movements observed during fetal deterioration. Cross-sectionalanalysis of median values (28-31 weeks gestation) did not revealdifferences in the quantity of general movements when IUGR, normalpregnancies and premature rupture of the membranes (with or withoutoligohydramnios) were compared. The quantity of fetal breathingmovements was significantly lower in pregnancies complicated by IUGRand by premature rupture of the membranes with oligohydramnioscompared to those of normal pregnancies and premature rupture of themembranes without oligohydramnios. In uncomplicated IUGR, thequantity of general movements and breathing movements was in thesame range as in normal uncomplicated pregnancies. Similar to thequality of general movements, the quantitative variables were related tothe fetal condition. However, in contrast to the quality of generalmovements, the quantity of general movements and breathingmovements showed a high inter- and intraindividual variation.Therefore, the results of this study discouraged the use of quantitativeaspects of general movements and breathing movements as reliableindicators of the neurological condition in the individual fetus (52). On theother hand Ribbert and coworkers showed that the assessment of fetalactivity may be of help in fetuses with a marginally reduced FHRvariation, in which prolongation of pregnancy is considered desirable toallow further maturation in utero (53). In order to determine changesoccurring with time they longitudinally studied fetal heart rate variation,general movements, breathing movements and haemodynamics in 19intrauterine growth restricted fetuses, who eventually were deliveredby caesarean section (CS) because of fetal distress. In 14 of 19 fetusesabnormal velocity wave forms were present from the beginning of thestudy onwards. FHR variation was initially just within or below thenorm and fell further during the last 2 days before CS. General movementsand breathing movements fell below the normal range later and in alower rate of occurrence than FHR variation. Fetal GM showed a more orless consistent fall in time, whereas fetal breathing movements (FBM) showed a wide range throughoutthe period of observation. The poorest outcome occurred in fetuses withreversed end-diastolic velocities and rapid fall in FHR variation. It wasconcluded that with progressive deterioration of the fetal conditionabnormal velocity wave form patterns occur first; FHR variation isreduced subsequently while GMs and FBM are the last to becomeabnormal (53). In another study fetal heart rate (FHR) variation and movements(FA) was investigated in 27 normally grown fetuses and in 18 fetuseswith intrauterine growth restriction (54). The results confirmedpreviously shown decrease of fetal movements in IUGR fetuses ascompared to normally grown fetuses at all gestation times. Theinvestigators reported that IUGR fetuses also spent a significantly lowerproportion of time exhibiting high FHR variation at 28-31 weeks. If thefetal movements were compared to FHR one can conclude that more ofthe IUGR fetuses had abnormalities of movements. Finally, within theIUGR fetuses, those with small head circumferences (less than 3rd centile)had lower movement rates during periods of both low and high FHRvariation, though this was only statistically significant for periods of lowFHR variation. This published report offered the possibility that objectiveevaluation of fetal behaviour could be used in a clinical setting andcould provide a more sensitive method of fetal assessment thanbiophysical profile scores (54).A causal relationship with the impairment of fetal oxygenation hasbeen suggested for a reduction in the incidence of fetal movements andin fetal heart rate variation. To test those hypothesis 16 IUGR fetusesand 13 normally grown fetuses were observed during maternalhyperoxygenation that was applied for 40 min in order to increase fetalPO_2 levels (55). All IUGR fetuses had abnormal Doppler blood velocitywaveforms of the umbilical artery suggesting an impaireduteroplacental exchange. The effect of hyperoxygenation on fetalbreathing and body movements and on fetal heart rate was evaluated.In the IUGR fetuses there was a significant increase in fetal breathingand body movements and in heart rate variation duringhyperoxygenation as compared to the preceding control period of 40min. No significant changes in fetal breathing and body movementswere found in the normally grown control fetuses. A surprisingobservation was the increase of the number of heart rate decelerationsafter discontinuation of the maternal hyperoxygenation. It wasconcluded that in IUGR fetuses the increase in fetal heart rate variationand the increase in the incidence of breathing and body movementsduring maternal hyperoxygenation substantiates the relationshipbetween these variables and the oxygenation status of the fetus.26 The implementation of 4D sonography was necessary to find outwhether the quantity of fetal facial expression and quality of bodymovements can be used as an additional diagnostic criterion for prenatalbrain impairment in fetuses with growth restriction. For that purpose aprospective study was conducted in 50 pregnant women with a growthrestricted fetus and in 50 uncomplicated healthy women in the thirdtrimester of pregnancy (56). 4D ultrasound observation was speciallydesigned to assess whether functional brain impairment and fetal growthrestriction had prenatally occurred by the utilization of several behavioralpatterns. The results showed that the median value of all movementpatterns

in the normal fetuses differed from fetuses with intrauterine-growth restriction (IUGR). Statistical evaluation revealed significantdifferences in the distribution of the movements between these groups.A tendency that IUGR fetuses have less behavioral activity than normalfetuses was noted in all observed movement patterns. Correlation reachedstatistical significance between normal and IUGR fetuses in the thirdtrimester in hand to head, hand to face and head retroflexion. Statisticallysignificant differences could be shown in the distribution of the medianvalues of observation over the five qualitative categories of head and handmovements. Using 4D sonography, this study has opened for thefirst time the possibility of visualizing the full range offacial expressions in the IUGR condition. The medianfrequency of all facial expressions in the IUGR groupwas slightly lower compared with the control group. These recent data on IUGR fetuses obtained by 4Dsonography are stimulating and might result in a more effective strategyto assess development before birth and may encourage future use of 4Dultrasound for quantitative and qualitative assessment of fetal behavioras 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 forebrainand 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 cerebralpalsy and intrauterine growth (66). Below the 75th weight centile the prevalence of cerebral palsy for males is statistically significantlygreater than that for females. At about the 90th centile the difference disappears. Male infants are according to some datas up to a month less mature atterm (and presumably also proportionately less mature at earlier gestations) thantheir female counterparts (67, 68). This maturity difference is specifically true forcerebral anatomy (lateralization (69) and myelination (70) and can be measuredas differences of in utero behavioral adaptation to evoked responses (67). Suchimmaturity might make male brains more vulnerable to insult at a variety ofstages including intrapartum stressors.There is also intriguing possibility that the optimum size at birth for malesis further from their population mean weight than is true for females. The rate ofcerebral palsy in males even at the 90th to 97th weight centiles is lower than for males of "normal" birth weight (25th to75th centiles), whereas for females, the reverse is true. As male infantsare significantly heavier than females, being further from optimum birth weightmay arise owing to maternal constraint, a limit to intrauterine growth rate createdby the limits of maternal resources which are reached earlier for the male infantthan for the smaller female infant (71). Recently published review deals with associations and confusions regarding IUGR and CP (62). In these article 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 90^{th} centile preterm weigh 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 sophisticatedaccount of relative size can be made using centile charts. It is important to pay attention that these cetntile charts are notout ofdate. With the average weight of healthy infants at birth increasing by up to50 g every 10 years (77, 78), progressively fewer infants are qualifying asSGA as defined by old growth charts. The centile charts may also haveinsufficient 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 arenot healthy in this sense but tend to be lighter (80) and slower growing (81) thanfetuses of the same post conceptional age, presumably for reasons related to theirpreterm birth. Because conventional "neonatal" birth weight standards are basedon the observed birth weights of infants born at different gestational ages, comparingthe weight of preterm infants with cerebral palsy with these standardscompares them with other preterm infants who themselves are more likely to beabnormally grown. To avoid this problem, the relative size of infants born beforeterm should be judged using reference standards based on the intrauterine weightfor gestational age ("fetal" standards) rather than birth weights. Such fetal standardsare derived from ultrasound-based estimates of the weights of healthyinfants in utero at known gestational ages (82, 83). The standards can be tailoredto 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 factorsthat 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 cerebralpalsy was not elevated for very preterm SGA infants. Reason for this could be that the neonatal growth standards and the controls used were equally biasedby the inclusion of an excess of abnormally light preterm infants. In addition, when fetal growth standards are used, there is a significant elevation of therisk for cerebral palsy for very preterm SGA infants in a similar pattern to thatwhich applies at term. Intriguing question is whether cerebral palsy is a consequence, or a cause of growth deviation, or simply an associatedphenomenon (62). Answer on this question can have direct impact on obstetricians. If the brain damageassociated with cerebral palsy precedes growth changes, recognitionof growth restriction occurs too late for preventative intervention. Furthermore, growth abnormality may be the first, albeit, crude signal that inutero pathology is occurring. This finding may indicate the need for furtherinvestigation with a view to potential in utero treatment (eg, of infections) ordelivery in optimal circumstances. If the risk for cerebral palsy is elevated as aconsequence of growth deviation, underlying causes ofgrowth 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 orearly neonatal period has been challenged and antenatal andunclassifiable factors are now considered as the most important etiologicfactors (23, 89, 90). Cerebral palsy is an "umbrella" term for disorders ofdevelopment, movements and posture, resulting in limitations ofactivity due to non-progressive impairment of developing brain (90). Thisdiagnosis describes a group of disorders of development of movementand posture, causing activity limitations that are attributed to nonprogressivedisturbances that occurred in the developing fetal or infantbrain. 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 purposelyvague because our understanding of developmental neurobiology isevolving rapidly. "Disturbances" is used as a comprehensive termreferring "to events or processes that in some way interrupt damage orotherwise influence the expected pattern of brain maturation" (91). Thoseevents or processes are many, with consequences varying from veryconspicuous to very subtle. The worldwide prevalence ranges from2 to 2.5 per 1000 live-births and the incidence did not change since1951, respectively. Improvement of obstetrical and neonatal care didnot result in decreasing prevalence rate of CP. On the contrary, theincidence and severity of CP increased due to a better survival rate ofvery immature and tiny premature infants with significant morbidityand increased number of risk factors. Cerebral palsy is the most commonchronic motor disability of childhood. The diagnosis is retrospectiveand it is rarely made before the age of six months when the infant isseverely affected. The specificity of the diagnosis improves as the childages and the nature of the disability evolves (91). CP does not result froma single event but rather from a sequence of interdependent adverseevents. This time frame of evolving adverse events should be takeninto account when considering the possibility of CP diagnosis ininfants (93). Periventricular white-matter injury is now the most commoncause of brain

injury in preterm infants and the leading cause of chronicneurological morbidity and CP. Standardized methods of clinicalneurological assessment from the neonatal period onwards weredeveloped in order to identify three grades of neurological impairment:severe, moderate and mild. The clinical identification of severelyaffected patients is less problematic than the identification of moderately- and mildly affected infants. Cranial ultrasound, magnetic resonanceimaging, magnetic resonance spectroscopy and diffusion weightedimaging are helpful in very low birth weight premature and in terminfants with encephalopathy (90).

From the pediatric experience it is well known that one should waituntil 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-disablingCP. This delay for the full clinical expression of functional consequencesof a brain damage depends on brain maturation. DiPietro was right insaying that a consensus recognizing the fact that fetal neurobehaviorreflects the developing nervous system is emerging (93-95). The purposesof early diagnosis of CP could be important from the point of view ofthe infant, the mother, the family, and the gynecologist, who is oftenaccused for clinical negligence. Although randomized studiesconfirming that the early intervention as an effective strategy fortreatment 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 theprenatal period (90, 92).

One crucial question often posed to neonatologists is to determinethe exact timing of brain damage, prenatal or intrapartum, in the contextof neonatal encephalopathy. In this perspective, repeated neurologicalassessments over the first days of life allow identification of two profiles.The first, a dynamic profile, is associated with signs of CNS depressionincreasing within the first 3 days and then decreasing gradually withobvious improvement in alertness, motor activity, and sucking (96). Thisprofile is typical of recent insult, most often intrapartum. The secondone, a static profile, is disclosed by lack of changes along repeatedassessments in the first week of life. This latter profile is typical of aprenatal insult that occurred in utero at least several weeks earlier andtherefore, already stable at the time of birth. In addition, theidentification of three signs already present at birth offers a preciousclue to fetal brain damage, when observed in a cluster:

- High-arched palate (due to insufficient molding forces of ahypoactive tongue),
- Non reducible adduction of the thumb in a clenched fist (due toabsence 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 palatewith 3D surface imaging since this technique does not permitvisualization of deep structure in the oral cavity. However, detectionof the two other signs as a specific expression of brain impairmentappears promising (Figure 3).

Development of Prechtl's general movements (GM) for postnatalneurological 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 infantsseemed especially attractive. Development of computer and ultrasoundtechnology enabled evaluation of fetal GM in three dimensions and inreal time (97, 98). GM includes the consideration of body movements (arms,legs, neck and trunk) spreading in variable sequences with gradualbeginning and end. They wax and wane in intensity, force and speed,being fluent and elegant, revealing the complexity and variability ofmotor activity already present even in early stage. GM has to bevideotaped and then analyzed based on

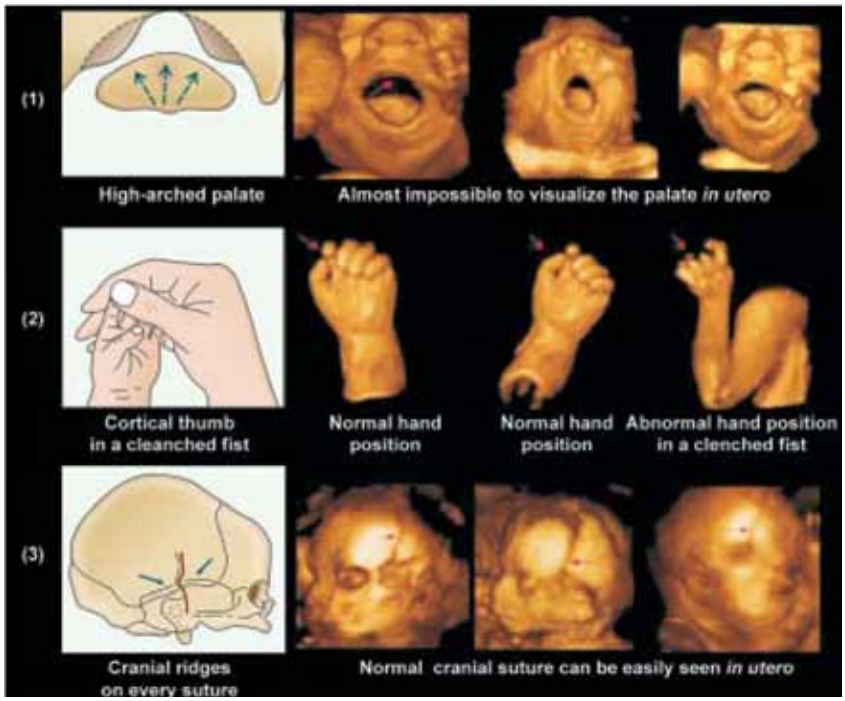


Figure 3. Neonatal signs indicating a prenatal insult (sketch pictures) and comparison with 3D-US imaging in utero. (1) High-arched palate (left) and 3D-US imaging of the entire oral cavity (right); (2) Cortical thumb in a clenched fist (left) and 3D-US imaging of the normal and abnormal hand position. (3) Cranial ridges on every suture (left) and 3D-US imaging of the normal cranial suture in utero.

visual "Gestalt perception",which provides an overall impression of GMs with standardizedprocedures (37). Subsequently, movement patterns will be described interms of complexity, variability and fluency. GMs will finally beclassified as normal-optimal, normal-suboptimal, mildly abnormal anddefinitely abnormal (96). While the application of GMs in postnatal life isstandardized and in spite of encouraging results of fetal GMs in the last 25 years which showed that qualitive assessment of GMs is a goodmarker of brain dysfunction, (32) they did not shift the diagnosis ofneurological impairment to the prenatal period.

The Amiel-Tison Neurological Assessment (ATNAT) relyes onresponses to specific maneuvers and has specific contribution in theexploration of passive and active tone according to neurologicalmaturation (99). The clinical significance of this type of assessment wasmore fully understood when Sarnat (100) reviewed anatomical andphysiological correlates of early neurological development. In fact, itbecame possible to clinically dissociate the development of upper andlower motor systems:

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

2. The upper system, consisting of the cerebral hemispheres and basalganglia, matures later (beginning at 32 GW) and rapidly for the first2 years in a descending wave; its essential role is to control the lowersystem, with relaxation of the limbs and control of the antigravityforces, finally allowing erect posture, walking and fine motor skills.

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

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

Some criteria observed in the fetus are only prerequisites for ex uterofunctional achievements: opening of the eyes for visual pursuit, facialexpressions for social interaction. Their identification by 4D imaging,in addition to efficient and rhythmic sucking supports the absenceof CNS depression.

Analytical criteria of typical passive and active tone in the neonatecannot be elicited in the fetus: head anteflexion versus retroflexion,ventral versus dorsal incurvations in the axis, both being of theutmost importance postnatally to confirm CNS optimality. However,optimality in the fetus should be reflected in typical GMS.

Criteria aiming to check autoregulation are slightly different: typicalnon stress test (NST) in the fetus and absence of reactions in theneonate.

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

- 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 goodinter-rater reliability with a Kappa coefficient of 0.76. As describedabove, the identification of "CNS depression" during fetal life is basedon pre-competences

	Neonate At 40 GWs	Fetus Between 20-40 GWs	
Optimality Criteria	ATNAT	Prechtl GMA 3D/4D-US	Significance
Head circumference Cranial sutures	Within normal limits Some range as other growth parameters Edge to edge, squamous included		Adequate hemispheric growth
Visual pursuit Social interaction Sucking reflex	Easily obtainable Eager	Opening of the eyes Facial expressions	Absence of CNS depression
	Efficient, rhythmic		
Raise to sit and reverse Passive axial tone Passive tone in limbs	Active flexion of the head Flexion ≥ Extension Within normal limits And symmetrical	Optimality should be reflected in typical GMs	Integrity of the upper motor control
Fingers and thumbs movements	Independent movements of fingers Active abduction of thumbs		
Autonomic control	No disturbance during the assessment	Typical NST	Stability of SNA

*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 pregnancie by 3D/4D sonography. (From 29)

(opening of the eyes, variety of facial expressions),primary reflexes (rhythmical bursts in the sucking pattern) and qualityof GMs. The addition of cranial signs (such as insufficient head growthand overlapping sutures) to neurological signs could be a valuablecomplement. Moreover, the identification of dynamic and static patternsof 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 areknown to occur in utero, abnormally rhythmic movements having beenoccasionally perceived and reported by mothers. However, it is unlikelythat such a brief and rare event should be seen with 4D-US.

An atlas on fetal CNS diseases recently reviewed fetal brain imaging;one chapter covers any visible congenital brain anomalies (101) whileacquired brain abnormalities in utero including destructive lesions dueto hypoxic-ischemic events, intracranial hemorrhage, porencephaliccysts and pseudocysts, are reviewed in another chapter (102). The probableoutcome may be estimated according to fetal age at the time of diagnosis,size and location of clastic lesions or structural abnormalities as well asto the degree of severity of functional consequences evaluated by4D-US. How to use that information still remains litigious in many cases,depending not only on ethical positions (personal or national) but alsoon expectations concerning the degree of cerebral plasticity at this earlystage. We understand morphologists and neurosurgeons that often referto a few personal cases with a favorable motor outcome despite verydestructive brain lesions: they optimistically conclude that morphologydoes not always correlate with neurodevelopmental outcome. On thecontrary, pediatricians and neuropsychologists involved in long termfollow-up studies certainly are less optimistic. For example, an infantborn with a massive destruction of the whole Sylvian artery territory inthe left cerebral hemisphere may look fine when he sits independentlyat 7 months or walks independently at 18 months. However, at age 7years with a confirmed diagnosis of hemiplegic CP, severe motordisorders are accompanied by disturbances of sensation, cognition,perception, behavior and a seizure disorder. As a conclusion, it is wiseto check down the road: for each specific type of fetal brain damage,appropriate decisions for a conservative management have to rely onseries including long term outcome measurements.

Neuropathologists know very well that the best radiologicaltechniques are not microscopes: many changes are below the limits ofresolution of neuroimaging. Reviewing fetal and perinatal brain damagesin 1998, (103) it was stressed the point that the group of children with normalimaging but non-optimal cerebral function presents an excitingopportunity to hypothesize correlations between neurocognitivedisabilities and subtle diffuse brain abnormalities. However, we mustrefine every method of fetal assessment (fetal neurology included) beforeproviding obstetricians with safe guidelines for the optimal managementof fetuses at risk of neurodevelopmental disabilities. The 3D/4D-USgives hope for better future fetal management.

As far as subtle brain lesions are concerned, pathological gliosis hasto be distinguished from PVL as a diffuse lesion of white matterassociated with an increase of hypertrophic astrocytes (positive withglial fibrillary acidic protein staining). When using routinely thisstaining, similar lesions are also detected based on the presence ofreactive astrocytes in the germinal matrix; the de-population of thistransient structure that can follow a hypoxic-ischemic event mayinfluence the later capacity to produce neuroblasts and glial cells. Inthe postmigratory phase during the second half of gestation, anothertransient structure, the subplate, appears to be the site of selectivevulnerability (104) with consequences on neocortex formation. The subplateis located between the cortical plate and the intermediate zone, reachingits maximal thickness between 22 and 36 GW. Each neuron will migrateinto the subplate which plays several important roles up to term.Programmed cell death, wiring, and synaptogenesis are active processesduring the second half of pregnancy, "processes that in some wayinterrupt, damage or otherwise influence the expected pattern of brainmaturation".71

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

Finally, it appears that when we consider not only CP, the tip of theiceberg, but the full spectrum of motor disorders, the moderate andmild clinical aspects are much more frequent than the severe ones. It isprobably 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 andCP on the one hand, and diffuse damage and negative imaging withmilder disabilities on the other hand. Those categories overlap, i.e., somecases of the CP are not associated with clastic imaging and some caseswith subtle motor disability (non-disabling CP) are associated with, forinstance, obvious scars of PVL. In conclusion, clinicopathologicalcorrelations are established statistically but have to be applied withcaution for

each individual case.

The main obstacle to early prediction of CP based on a functionalobservation 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 hemisphericbrain damage, based on the observation of motor and reflex activityunder the control of lower structures? The clinician is able to follow theswitch in neural circuitry observed for each motor acquisition accordingto a specific chronology. As most of the hypoxic-ischemic damages ofminor and moderate degrees are located in the cerebral hemispheres, itseems unwise to expect reassurance about the integrity of upperstructures based on precompetent functional stages. Nevertheless, itremains important to test the integrity of the lower system as aprerequisite for a favourable outcome. This dilemma is not specific toneuromotor function. For example, fetal habituation which has attracteda lot of attention as a potential means of assessing fetal neural integritymay just be a prerequisite depending on the lower system (105). More longterm data are necessary to establish its predictive value for laterdevelopment.

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

One of the most promising improvement in the unknown fieldof prenatal behavior has been the new 3D/4D-UStechnology. Its advance has been completed in givingvisualizations in almost realtime and production of standardsfor different movement patterns to appear and develop. The4D study of fetal behavior provided us with a great possibilityof understanding the hidden function of the developmentalpathway of the fetal CNS and the potentialities of originatinga neurological investigation in utero. By 4D technology wemight be able to visualize an intrauterine neurologicalcondition that would enable to identify which fetus is atrisk and which is not. Existence of motoric competence inthe newborn, even preterm infants is assumed to have itsorigins in prenatal life. Behavioral perinatology assessed by4D sonography should be an interdisciplinary area ofresearch involving concepts and conducting studies of thedynamic interplay between behavioral processes in fetal,neonatal, and infant life. The ultimate clinical application offetal neurobehavioral assessment will be to identifyfunctional characteristics of the fetus that predict a rangeof subsequent developmental dysfunction. Establishing thislink will require demonstration of positive and negativepredictability to outcomes significantly beyond theimmediate perinatal period. After standardization of validreference ranges of movements appropriate for thegestational age, attempts have been made to produce a newscoring system for fetal neurobehavior based on prenatalassessment by 3D/4D sonography (106, 111-114). That preliminary workmay help in detecting fetal brain and neurodevelopmentalalterations due to in utero brain impairment that isinaccessible by any other method.

In the recent study, the Zagreb group published a newscoring system for fetal neurobehavior based on prenatal assessmentby 3D/4D sonography (106). That scoring system is a combination of someparameters from fetal GM assessment and parameters from postnatalATNAT which can be prenatally easily visualized by 4D-US (107, 108). Theparameters were chosen basing on developmental approach to theneurological assessment and on the theory of central pattern generatorsof GM emergence. They were the product ofmulticentric studies conducted during several years which resulted withthe most significant parameters for the assessment of fetal neurologicaldevelopment (Table 4). (42, 109, 110).

The authors developed a threepointscale for isolated head anteflexion, isolated hand, leg, hand to face andfinger movements, while for the assessment of cranial sutures, isolated eye blinking, facial alterations and mouth opening two-point scale wasapplied. The distinction between scores 0 and 2 is evident, whereasuncertainty may exist with regards to the assignation of a score of 1,the latter indicating an abnormal result of moderate degree. The precisedescription 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 severelybrain damaged infants and those with optimal neurological findingsby comparing fetal with neonatal findings. In the group of 100 low-riskpregnancies they retrospectively applied new scoring system. Afterdelivery, postnatal neurological assessment (ATNAT) was performed (95) and all neonates assessed as normal reached a score between 14 and20, which was assumed to be a score of optimal neurologicaldevelopment. New scoring system was applied in the groupof 120 high risk pregnancies in which, based on postnatal neurologicalfindings, three subgroups of newborns were found: normal, mildly ormoderately abnormal and abnormal. Based on this, a neurologicalscoring system has been proposed. All normal fetuses reached a scorein the range from 14 to 20. Ten fetuses who were postnatally describedas 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 hypertensive hydrocephaly,one had tanatophoric dysplasia and four fetuses had multiplemalformations.

Based on several years of research that group of authors hasproposed a new test for antenatal application. There is a similaritybetween neonatal optimal-

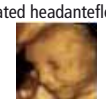
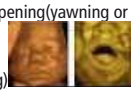
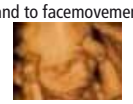
Sign	Score			Sign Score
	0	1	2	
Isolated headanteflexion 	Abrupt	Small range(0 – 3 times ofmovements)	Variable in full range, many alternation (> 3 times of movements)	
Cranial sutures andhead circumference 	Overlapping of cranialsuttures head circumferencebelow or above the normal limit (-2SD) according toGA	Normal cranialsutures normal head circumference		
Isolated eye blinking 		Not fluent(1 – 5 times ofblinking)	Fluency(> 5 times of blinking)	
Facial movements(grimace or tonqueexpulsion) 		Not fluent(1 – 5 times ofalteration)	Fluency(> 5 times of alteration)	
Mouth opening(yawning or mouthing) 		Not fluent(1 – 3 times ofalteration)	Fluency(> 3 times of alteration)	
Isolated hand movement 	Cramped	Poor repertoire	Variable and complex	
Isolated leg movement 	Cramped	Poor repertoire	Variable and complex	
Hand to facemovements 	Abrupt	Small range(0 – 5 times ofmovement)	Variable in full range, many alternation (> 5 times of movements)	
Fingers movements 	Unilateralor bilateral clenchedfist, (neurological thumb)	Cramped invariablefinger movements	Smooth and complex, variable finger movements	
Gestalt perception ofGMs	Definitely abnormal	Borderline	Normal	
			Total score	

Table 4. Antenatal Neurological Screening Test (KANET)

ity test of Amiel-Tison, and that new scoringsystem for the assessment of neurological status in fetuses, which is acombination of postnatal ATNAT and GM assessment (100). One of the differences was that the analytical criteria of typical passive and activetone in the neonate cannot be elicited in the fetus: head anteflexionversus retroflexion, ventral versus dorsal incurvations in the axis, bothbeing of the utmost importance postnatally to confirm CNS optimality.However, the status of the fetus should be reflected in the typical GMs.

The potential of the test was investigated at four university departments. The objective of this multricentric study (111) 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.

TOTAL SCORE	INTERPRETATION
0-5	Abnormal
6-13	Borderline
14-20	Normal

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

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, thrombophylia, 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, thrombophylia, preeclampsia, achondroplasia, 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-

FAMILY HISTORY	previous child with cerebral palsy
MATERNAL CONDITION	diabetes mellitus type I and II, thyroid disease, preexistent hypertension, drug abuse, thrombophilia, anemia, epilepsy,
PREGNANCY RELATED DISORDERS	gestational diabetes, Rh immunization, threatened preterm labor, preeclampsia, intrauterine infections, viral illness, cholestasis
FETAL CONDITION	structural and chromosomal abnormalities, polyhydramnion, intrauterine growth restriction, pathological findings in electrical fetal heart monitoring or Doppler findings,

Table 6. Inclusion criteria for high risk pregnancies

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 (artrhoghryposis, vermis 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, tong 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 KANET and ATNAT tests. In practical sense, it means that the neuropediatrician who examined the newborns with ATNAT test confirmed 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 overestimated nor underestimated.

8. CONCLUSION

Despite medical reports from 100 years ago and 25 years of systematicresearch initiated by Prechtl and colleagues, the study of prenatalbehavior is still in its infancy. One of the most promising advances inthe field of ultrasonography has been the new 4D-US technology. Itsadvance has been completed in giving visualizations in almost realtime.The availability of new diagnostic data has in an extraordinaryway raised our knowledge about intrauterine life, substantiallymodifying some earlier interpretations.The 4D study of fetal behavior provided us with a great possibilityof understanding the hidden function of the developmental pathwayof the fetal CNS and the potentialities of originating a neurologicalinvestigation *in utero*. Now, by 4D technology, we might be able tovisualize an intrauterine neurological condition that would enable toidentify which fetus is at risk and which is not. Existence of motoriccompetence in the newborn, even preterm infants is assumed to haveits origins in prenatal life. Behavioral perinatology assessed by 4Dsonography should be an interdisciplinary area of research involvingconcepts and conducting studies of the dynamic interplay betweenbehavioral processes in fetal, neonatal, and infant life. The ultimateclinical application of fetal neurobehavioral assessment will be toidentify functional characteristics of the fetus that predict a range ofsubsequent developmental dysfunction. Establishing this link willrequire demonstration of positive and negative predictability tooutcomes significantly beyond the immediate perinatal period. Afterstandardization of valid reference ranges of movements appropriatefor the gestational age, attempts have been made to produce a newscoring system for fetal neurobehavior based on prenatal assessmentby 3D/4D sonography. That preliminary work may help in detectingfetal brain and neurodevelopmental alterations due to in utero brainimpairment 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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Corresponding author: Prof Asim Kurjak, MD, PhD. Department of Obstetrics and Gynecology, University Hospital "Sveti Duh", Medical School, University of Zagreb, Zagreb, Croatia.