NEUROLOGICAL ASSESSMENT BY 4D SONOGRAPHY IN HIGH RISK PREGNANCY

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INTRODUCTION

Assessment of the integrity of the fetal nervous system is a major task in perinatal medicine. There have been many attempts to achieve this goal although most have concentrated on risk factors which could impair the central nervous system (CNS). Signs of hypoxia as reflected in the fetal heart rate and heart rate variability, pulse oxymetry and Doppler measurements of cerebral blood flow have raised great interest, but direct assessment of the functional condition of the fetal nervous system was not possible (1,2,3).

Fetal behavior can be defined as fetal activities observed or recorded with ultrasonographic equipment. As it is not yet possible to assess functional development of the CNS directly, investigators started to analyze fetal behavior as a measure of neurological maturation (4).

A rapidly accumulating body of evidence has proved that the spontaneous motility of fetuses, preterm, and term infants as well as infants during their first months of life has great clinical significance. It proves to be an important functional indicator of brain dysfunction at a very early age. From the repertoire of movement patterns the so-called general movement, the most frequently occurring and most complex pattern, were selected for diagnostic purposes (5,6).

Preeclampsia has been recognized as a potentially fatal complication of pregnancy for more than a century. It complicates between 3% and 10% of pregnancies and is responsible for a large portion of maternal and perinatal morbidity and death (7,8). Despite extensive research into the causes and pathogenesis of this condition, delivery of the fetus and placenta is still the only effective treatment. Specifically, evidence of chronic fetal compromise, such as intrauterine growth restriction, has been used by some, but not others, to preclude expectant management (9,10). Obstetric management of the IUGR fetus is complex and is based on presumed cause of the altered growth, gestational age, and predicted neonatal outcome. Reported neonatal outcomes are often confounded by inclusion of neonates with significant and life-threatening anomalies and chromosomal defects (11,12). Obstetric decision making regarding antenatal testing, intrapartum evaluation, and timing and route of delivery is often based on the perception of likelihood of survival and major morbidities, which for growth restricted infants may be considerably different than with their normally grown counterparts

It is understood that the growth restricted (IUGR) fetuses moved less, but in individual cases an overlap existed with control fetuses. There was a reduction of both number and duration of general movements in the IUGR group. The qualitative analysis of general movements revealed a reduction of the quicker components leading to slow and monotonous movement patterns (13).

Observation of spontaneous movements in the unstimulated infants led to the suspicion that general movements of high-risk infants look different from those of normal infants (6). The first study of this method was concerned with severely IUGR fetuses (13).

Their general movements were poorly organized and sluggish. Because in some cases of IUGR the complexity of general movements was impaired as well, this was taken as a sign of brain dysfunction (14,15).

The effect of documented brain damage on the quality of general movement developmental trajectories and long-term outcome was investigated systematically by Ferrari and co-workers (16). The great advantage was, that in the mild cases general movement assessment differentiated between the infants with bad outcomes and those with good outcomes. That general movement assessment is superior to the traditional neurological examination was shown for preterm infants and for full-term infants (17-19). The predictive power of general movement assessment for neurological and developmental outcome is clearly higher (6).

Three-dimensional (3D) ultrasound has been available for more than 10 years. However, the 3D image freezes the object and therefore does not provide information on movements or any information about the dynamic changes of the object of interest (20). A technique was needed that would enable 3D imaging to be performed in a real-time mode. This technique is recently introduced and called four-dimensional (4D) sonography, because time becomes parameter within the 3D imaging sequence (21). This new diagnostic tool is enabling the continuous monitoring of the fetal face and other surface features of the fetus such as fetal extremities, thus opening up exciting new possibilities for the study of the completely unexplored area of fetal behavior as a possible measure of neurological maturation.

In particular, four-dimensional ultrasound (4D US) provides a new tool for observation of fetal face (22). Simultaneous imaging of complex facial movements was impossible using real-time 2D sonography. 4D US integrates the advantage of the spatial imaging of the fetal face with the addition of time. This novel technology therefore allows the appearance and duration of each facial movement and expression to be determined and measured (23). In a relatively short period of time 4D US stimulated many multicentric studies on fetal behavior and even fetal awareness with more convincing imaging and data than those obtained by conventional ultrasonic and non-ultrasonic methods. It is the purpose of this article to review and illustrate presently available data on fetal behavior in all three trimesters of pregnancy.

FETAL BEHAVIOR AS POSSIBLE SCREENING PROCEDURE FOR NEUROLOGICAL DEVELOPMENT IN UTERO

Some attempts have been made to initiate a prenatal screening system in order to discriminate fetuses from the general population with compromised CNS function (24). The development of movement patterns has been described as a major maturational process and a sensitive indicator of neurobehavioral organization and future temperamental and cognitive status. The real breakthrough in the analysis of fetal movement patterns was due to the introduction of high quality ultrasound equipment which enabled the observer to carry out real-time observations with sufficient dynamics and good image resolution. (Figure 1)
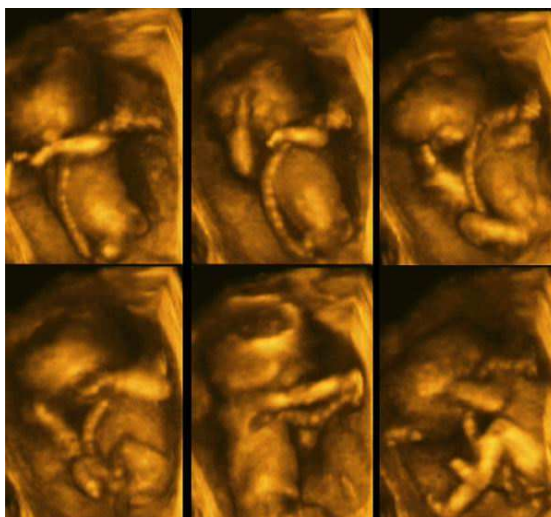
Figure 1. 4D continuous sequence of the fetus at 12 weeks of gestation showing general movements. The complex movements of the limb, trunk and head are clearly visible and cause a shift in fetal position. In the first sequence, the right hand is flexed in elbow joint. In the next sequence, the fetus raised the hand and began to deflect in elbow joint. In the last sequence, further elevation of hand is seen

The very first movements seen in any fetus are slow extensions of the neck at 7-7.5 weeks (Figure 2). They are present for a few days and are then followed by the occurrence of startles and general movements. While the first type consists of a rapid phase contraction of all limb muscles, often with secondary involvement of neck and trunk muscles, the latter are complex movements involving neck, trunk and limbs. They vary in speed and are forceful but fluctuating in intensity (25).
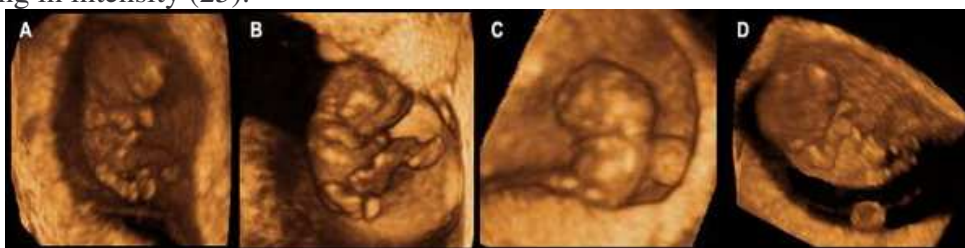

Figure 2. Fetus at 7-8 weeks of gestation. Note the extension of the neck. The fetal hands are located in front of chest and no movements of wrist and fingers are visualized

After the ninth gestational week the repertoire expands rapidly. Hiccups appear, often in series, for up to several minutes, and isolated arm and leg movements can be observed (Figure 3).
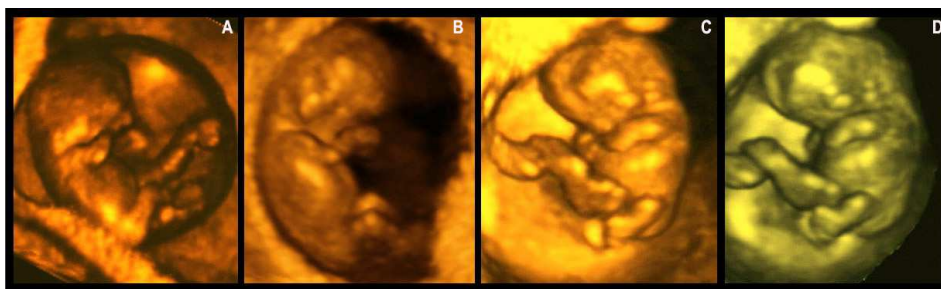
Figure 3. Fetus at 8-9 weeks of gestation. Isolated hand movements in front of the chest are visualized. Note the wrist and fingers are on the same level

This is remarkable in two respects. First, that the young fetus is able to perform isolated movements of one limb at an age when one would expect a longer period of diffuse and generalized motor activity. The second is the unexpected finding of the simultaneous onset of arm and leg movements, unexpected because of the long held principle of a cephalocaudal development in spinal motor functions (23-25). After ten weeks, head movements of various types can be seen. They consist of lateral rotation of the head and overextension of the neck (Figure 4).

Figure 4. Fetus at 10-11 weeks of gestation. The fetal hands are moving directly to the face. Note the movements of wrist and fingers are depicted and also lateral rotation of the head is clearly visibled.

These movements are carried out with moderate speed and occur in isolation. At about the same age, hand-face contact is seen for the first time. Usually, this is an accidental contact of a hand with the face or the mouth. Between 10.5 and 12 weeks the fetus starts to make breathing movements. At 11 weeks three new patterns, namely the opening of the jaw, bending forward of the head and complex stretch movements, are added to the repertoire.

Somewhat later than the irregular jaw movements, yawns occur. These have the same pattern as in children and adults and hence are easily recognizable. The same holds true for the most complex stretches, which also retain an identical movement form into adult life. At 13 weeks, rhythmical sucking movements, often followed by swallowing, occur in bursts (23-25). The rate of these sucking movements at 14 weeks is already about the same as in term infants during breastfeeding. Fetal drinking regulates the amount of amniotic fluid (Figure 5).

Figure 5. 4D continuous sequence demonstrated fetal drinking and rhythmical sucking movements

After fetal eye movements (Figure 6) were discovered by Bots and co-workers (26), Birnholz reported the onset of slow, rolling eye movements at 16-18 weeks followed by rapid eye movements at 20-22 weeks which include also nystagmoid movements (27). During the second half of pregnancy hardly any new movement patterns emerge (28).

Figure 6. 3D surface rendering demonstrated fetal eyelid opening

In studies on the relationship between fetal motor behavior and the development of the central nervous system, general movements have proved to be of major importance, due to their early emergence, frequent occurrence, and complexity (29,30). According to the definition, general movements are motor patterns in which all parts of the body are involved and which may last from a few seconds to a minute . The sequence of arm, leg, neck and trunk movements which follow each other within one general movement is variable. The character of general movements remains essentially unchanged from their emergence until the second month after birth at term. The early emergence of general movements and consistency in pattern provoked research on the clinical significance of fetal movements in the assessment of the integrity of the fetal central nervous system (29,30). For this purpose, studies were performed on fetal motor behavior during undisturbed, low risk pregnancies, in which fetal motor behavior was analyzed with respect to the quantity and the quality of the movements (29,30).

Assessment of Fetal behavior

Fetal behavior can be defined as fetal activities observed or recorded with ultrasonographic equipment (4). As it is not yet possible to assess functional development of the CNS directly, investigators started to analyze fetal behavior as a measure of neurological maturation (4). For the first tirne, studies of spontaneous prenatal movements and behavior in utero were performed and published. Since fetal body movements give important information about the condition of the fetus, their quantitative as well as qualitative aspects were analyzed. Zagreb group evaluated the advantages of 4D US over 2D sonography in the assessment of early fetal behavior (21). The observed body movements consisted of changing of the position of the head towards the body. With transvaginal 4D sonography, we found body movements at 7 weeks of pregnancy (Table 1) (21). Therefore, this technology enables the visualization of the moving phenomenon 1 week earlier than 2D ultrasound. At 7 weeks of gestation the dominant embryonic feature is the head, which is strongly flexed anteriorly. Upper and lower limb buds are visible on the lateral aspects of the embryo. However, embryonic movements are not frequent and consist mainly of moving of the head towards the rest of the body. At 8-9 weeks, the head is less flexed and the changes of the position of the head towards the body are clearly visible (21).

Table 1. The incidence of spontaneous embryonic/fetal movement according to gestational age

Gestational age (weeks)	CRL (mm)	No movements	Gross body movements	Limb movements	Complex limb movements
7-8	0 – 15	31	12	0	0
9-10	16 – 30	26	11	7	0
11-12	31 – 50	19	16	12	8

CRL crown-rump length
Adapted from reference 2

Furthermore, 4D US seems to be the method of choice for detecting subtle changes such as superimposed rotations and changes in direction of the movements These additional components make the movements fluent and elegant and create the impression of complexity and variability. These characteristics can be altered in fetus with anencephaly (31). The range of the movements occurs with forceful, monotonous, rigid and jerky in character in anencephalic fetus (Figure 7). Qualitative alteration of general movements (Figure 8) can be used as a marker of the severity of associated neurological disability.

Figure 7. 4D sequence of anencephalic fetus at 19 weeks of pregnancy, only hand to head movement in one direction of the left arm could be seen, their onset was abrupt and jerky. Body movements in anencephalic fetus showed lack of positional changes, and it occured abnormal, showing a waxing and waning in intensity. Using this technique, the function of lower

level CNS responsible for these forceful, monotonous changes are evaluated.

Figure 8. 4D sequence of normal fetus at the same age as Figure 10, hand movement could be observed in any direction. We can see head movement (retroflexion and rotation) followed by palm opening position simultaneously. Qualitative alteration of movements can be used as a marker of the severity of associated neurological disability.

Our recent study has shown that during the second and third trimester it is possible to study total fetal behavioral activities. In addition to yawning, sucking and swallowing described by 2D real-time imaging, it is now possible to study a full range of facial expressions including smiling, crying, and eye-lid movements (32). This may stimulate multicentric studies of the fetal behavior and responsiveness as a sign of neurological maturation. In the long term fetal behavioral studies may become a mean of assessing fetal well-being (32). Such a collaborative study is under way in Zagreb, Barcelona and Malaga.

Our group have been evaluating fetal behavioral patterns in the third trimester between 30-33 weeks of gestation in 10 gravidas (32). It is evident that eyelid and mouthing movements dominate at this gestational age. The continuity between fetal and neonatal behavior have been published recently from Zagreb, Barcelona and Malaga groups (33,34).

Assessment of Fetal movement

Sparling and Wilhelm described spontaneous movements in fetuses from 12 to 35 weeks of gestation and recorded the characteristics of hand movement (35). Many movements appeared to be directed to a body part or the uterine wall. The hands of the fetuses moved with a variety of frequencies and apparent force. During later gestational periods, the fetuses' hands were directed to and manipulated body parts and features of the environment, such as the umbilical cord.

Other developmental tendencies in hand movement were noted in early observations (33,34). In that study, movements such as thumb in mouth and bilateral leg extension against the uterine wall were considered by the authors as functionally important. The frequently observed leg extension against the uterine wall was believed by the authors to be a possible precursor to later participation in the birthing process. Early movements of the arms appear to assist the fetus in identifying components of its environment. Attributing function to any of these early movements, however, does not imply that the assigned function is preliminary to or necessary for the appearance of a spontaneous behavior (33,34,36).

Classification of movement patterns
In the classic paper, de Vries and co-workers classified at least to 13 different movement patterns (30).
1. Just discernible movements (between 7 and 8.5 weeks)
2. Startle.

3. General movements (Figure 1).
4. Hiccup
5. Breathing
6. Isolated arm or leg movement
7. Isolated retroflexion of the head
8. Isolated rotation of the head
9. Isolated anteflexion of the head
10. Jaw movements
11. Hand-face-contact : In this pattern of movement, the hand slowly touches the face, the fingers frequently extend and flex (Figure 9).
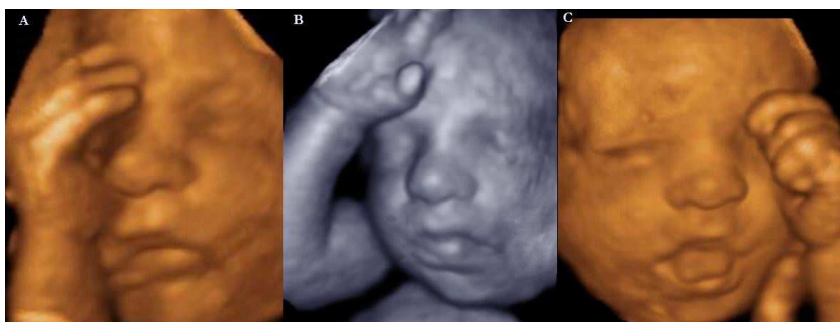12. Stretch (Figure 1)
13. Rotation of the fetus

Figure 9. Several 3D images of hand direction to the face (a), to the head (b), to the eye (c)

Assessment of fetal facial expression
Our group attempted to evaluate 4D US in the assessment of fetal facial expression. We had classified several facial expressions at least to 8 different activities (23,24).

Classification of facial patterns
1. Yawning (Figure 10).
2. Swallowing
3. Sucking
4. Smiling (Figure 11)
5. Tongue expulsion
6. Grimacing (Figure 13)
7. Mouthing (Figure 12).
8. Isolated eye blinking (Figure 6).

Figure 10. Yawning expression of the fetus. An involuntary wide opening of the mouth, with maximal widening of the jaw, and long and deep air inhalation through the mouth and nose followed by a slow expiration.

Figure 11. Several facial expressions characterized by turning up the corners of the mouth shows the smiling fetus.
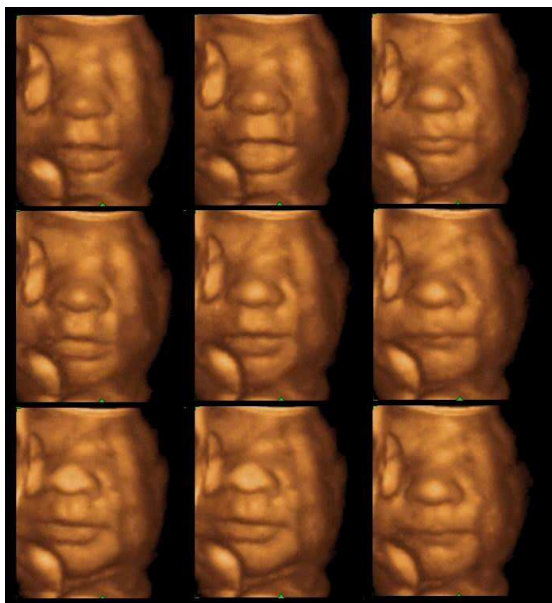

Figure 12. On this 4D sequence, mouthing could be observed as a facial expression pattern. We can se a series of rhytmic movement involving the mandible and tongue, characterized by constant frequency and duration until dissapearance.

The existence and relationships among these components is a large area for 4D sonography study in the psychological and fetal behavioral sciences. Facial expressions are an important channel of nonverbal communication. The characteristics of facial expressions can provide different mode to the expert for understanding the hidden side of the fetus in utero, a side which may not be accessible in the form of any verbalizations. We believe that the fetal facial expressions and fetal behaviors related to emotion can reveal part of the feeling side of a mothers's life (25).

The study of fetal facial expressions has many aspects. 4D ultrasound technology is the first new way of obtaining and analyzing its role in art, nonverbal communication and the possible emotional process between the explorer and the fetus. Many questions about fetal facial expressions remain unanswered and some areas are relatively unexplored. However, to get the answers to some of these unexplored area, we have to wait for further improvements in 4D technology and more multicentric studies.

NEONATAL ASSESSMENT

The aim of the recent multicentric research project is to find out whether pathological movement patterns in the fetal period are continuing in the neonatal period and which of them are predictable for the developmental impairment in infants and toddlers. Numbers of data are supporting the fetal origin of neonatal behaviour (33,34). It was assumed that individual differences in motor activity level in the first month following birth probably arise during fetal life, and existence of fetal-to-neonatal continuity for numbers of leg movements per minute was proved. Fetal state organization reflects the development of the central nervous system and is a stable individual attribute indicating the postnatal state organization. Fetal movement patterns could reflect the emotional state of the fetus and they can predict how much they are likely to cry postnatally (Figure 12).

Figure 13. The emotional state of the fetus prenatally can predict how much they are likely to cry postnatally. Note the fetal facial expression (grimacing) demonstrated in utero (below) using 4D technique is similar to the neonatal period (upper)

WORK IN PROGRESS

Recently multicentric study of fetal brain function in normal and high risk pregnancy has been established. The goal of this long term study is to investigate whether the prenatally detected abnormal behavioral pattern increases the number of newly discovered prenatal brain function

impairment. We will use 4D US for detailed evaluation of type and quality of fetal movements. Aim of usage of 4D is to find out whether the quality of peripheral and body movements and fetal facial expressions can be used as an additional diagnostic criteria for prenatal brain impairment. Furthermore, other goals are to differentiate prenatal and perinatal brain damage, find out its costs and economic justability, and finally, to evaluate the value of its nation-wide application. Gravidas from high risk group will be subjected to extensive ultrasound observation, especially designed to assess whether functional brain impairment had prenatally occurred by the utilization of above mentioned different behavioral patterns.

CONCLUSIONS

Understanding technical aspects of 4D US is important either for proper using of 4D or for obtaining its full potential. Furthermore, image post-processing should be considered as a part of examination. Sometimes, an additional information about the range of interest can be provided with post-processing. The study of fetal behavior provided us with an important contribution to understanding the hidden function of the developmental pathway of the fetal CNS and the potentialities to originate a neurologic investigation in utero. However, there are a lot of unknown factors and many challenges for open minded people. Indeed, an evolving challenge for the medical profession is to better define normal and abnormal fetal neurological function in utero so that we can better predict antenatally which fetuses are at risk for adverse neurological outcomes irrespective of intrapartum management.

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