Fetal Behavior in Normal Pregnancy and Diabetic Pregnancy
1Asim Kurjak, 2Sonal Panchal, 3Selma Porovic

ABSTRACT

Ultrasound (US) has been the modality of choice for assessment of the development of the embryo and fetus in the womb. Three-dimensional US has made the study of the fetal anatomy even more accurate and understandable. But fetal development is not only the development of the structures but also their functionality. The functionality of the kidneys, e.g., can be confirmed by urine production and filling of the bladder, the functionality of the bladder by its periodically emptying and filling, and that of the heart by fetal circulation. The function of the nervous system is the most complex and this can be studied by fetal movements and fetal expressions. The development of fetal motor behaviors can be studied by real-time US.1 The fetal activity observed or recorded with US equipment is fetal behavior.2

Study of the fetal movements has been found to be more correlating with the fetal central nervous system (CNS) development. Studies have shown that the development and maturation of the fetal nervous system is reflected by quality and quantity of fetal movements.3,4 On comparing the fetal movements with morphological studies, it was found that the fetal behavioral patterns directly reflected the development and maturation of fetal CNS. Therefore, assessment of fetal behavior in different periods of gestation can help to distinguish normal brain from abnormal during different phases of development.5 It also helps to make the diagnosis of functional and structural abnormalities earlier.6 B-mode or a two-dimensional (2D) US is impossible to understand the complexity of these movements and so till the invention of four-dimensional (4D) US it was not possible to correctly evaluate the fetal movements, especially fetal expressions. The details of fetal face and hands studied by 4D US have potential to generate information regarding fetal movement and behavior.7 There is a specific fetal behavioral pattern that corresponds to each week or trimester of fetal life and this pattern reflects the steps of human brain development and maturation.8-10

Keywords: Diabetic pregnancy, Fetal behavior, Kurjak’s antenatal neurodevelopmental test, Normal pregnancy.


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UNDERSTANDING THE NORMAL FETAL ACTIVITY

Spontaneous fetal movements can be observed using 2D US around eighth gestational week, but 4D US may show fetal motility at seventh week of gestation on transvaginal scans.11,12 From 10 weeks onward the frequency of fetal movements increases and are maximum between 14 and 19 weeks.12 The longest interval between movements at this age is 5 to 6 minutes. Between 9 and 14 weeks of fetal age, mostly general movements (GMs) are observed.13 Using 4D sonography, Kurjak et al14 found that from 13th gestational weeks onward, a “goal orientation” of hand movements (Fig. 1) appears and a target point can be recognized for each hand movement. At 15 weeks, 15 different types of movements have been recorded.15 But according to a study by Kurjak et al,16 16 different types of movements can be observed at 15 weeks of gestation. Eye movements are detectable at 16 to 18 weeks, organized complex movements at 20 weeks, and facial expressions also start at 20 weeks.17 Facial expressions like smiling, yawning, eyelid movement, mouthing, grimacing, tongue expulsion/swallowing, and sucking were observed during second and third trimesters. Mouthing was the most frequent facial movement during early third trimester, whereas scowling and sucking were the least frequent.15-18 In the second half of pregnancy, the frequency of GMs gradually decreases, particularly during the last 10 weeks of pregnancy.19 In the last trimester of gestation, the range of hand and face movements is the widest.19 Fetal neuromuscular development is due to alternate periods of increased and decreased movements, though the exact functional significance of the same is still not understood.20,21

The movement in an unstimulated fetus is the result of spontaneous behavior without sensory stimulation and is the best method to assess its CNS capacity,5 and can be used as a marker for fetal brain status.22 Any fetal brain insult will interfere with endogenous motor activity of the fetus. Genetic factors, external stimuli, pathological conditions, or even environmental changes can affect the fetal human brain up to a degree that may be difficult to assess, especially prenatally. Most of the times, the neurological damage and its effects are difficult to predict.23 Establishment of neural connections as a developmental process leads to development of new movement patterns of fetus or transformation of existing patterns.24

Integrity of the fetal CNS can be assessed by behavioral states of the fetus, viz., movement of individual organs...
like head, trunk, or limbs in an unstimulated but awake fetus and also by qualitative assessment of GMs. When fetal behavior is studied by 4D US, the altered movement pattern can diagnose abnormal brain development and assist early diagnosis of various abnormalities.

The centers in the cerebellum impose controls on the unrestricted movements induced by the lower centers of the brain. The movements also become more complex as pregnancy advances, which represents the cerebral maturation. Inhibition is a marker of neurological development (especially cortical centers) and most longitudinal studies have also proved that the fetus becomes less active as gestation advances. Movements observed and analyzed in second and third trimesters are shown in Table 1.

The spinothalamic tract is established at the 20th week and myelinated by 29 weeks of gestation and the thalamocortical connections penetrate the cortical plate at 24 to 26 weeks. Evoked potentials can be detected from the cortex at the 29th week, indicating that the functional connection between periphery and cortex operates from that time onward. This is because of maturation process in the brainstem. Facial expressions are representation of the maturation of the brain. Expressions like grimacing, tongue expulsion, and eyelid movements (Fig. 2) similar to emotional expressions in adults can be seen by 4D US.

General movements or gestalt perception involve the whole body in a variable sequence of arm, leg, neck, and trunk movements. The movements increase and decrease in intensity, but are fluent and elegant, complex, and variable. These are called fetal or preterm from 28 to 36, and to 38 weeks of postmenstrual age. General movements are considered to be a better predictor of Table 1: Types of hand and facial movements in fetus

<table>
<thead>
<tr>
<th>Hand and head movements</th>
<th>Facial expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head retroflexion</td>
<td>Isolated eye blinking</td>
</tr>
<tr>
<td>Head rotation</td>
<td>Mouthing</td>
</tr>
<tr>
<td>Head anteflexion</td>
<td>Yawning</td>
</tr>
<tr>
<td>Hand to head direction</td>
<td>Tongue expulsion</td>
</tr>
<tr>
<td>Hand to eye</td>
<td>Grimacing</td>
</tr>
<tr>
<td>Hand to mouth</td>
<td>Swallowing</td>
</tr>
<tr>
<td>Hand to face</td>
<td></td>
</tr>
<tr>
<td>Hand to ear</td>
<td></td>
</tr>
</tbody>
</table>

Figs 1A to C: This series of three pictures shows three different positions of hand (A to C) as three instances of the entire movement of hand to face.
postnatal neurological disability than clinical neurological examination alone.33

Normal GMs are complex but fluent and involve neck, trunk, and limb movements. Moreover, these should also increase and decrease in their intensity.34 General movements are complex and fluent and also are not repetitive.35 If that is not the case, they are considered abnormal.15,35 Slow, monotonous repetitive movements mimicking cramps are abnormal movements. Even when the movements are occurring with generalized simultaneous muscle contractions and relaxations, it is considered abnormal pattern.5,22 These also may show variability in strength and the amplitude of movements.22 These are often seen in the fetuses of mothers with diabetes mellitus, and also other pregnancies at risk like intrauterine growth retardation (IUGR), pregnancy-induced hypertension, and prematurity.15 Both term and preterm newborns, who had cerebral insult of any type during their prenatal period may also show abnormal general movement.11 The identification of fetal CNS depression is based on precompetencies (opening of eyes, variety of facial expressions) along with the primary reflexes (rhythmical bursts in the sucking pattern) and quality of GMs.5,36

Evaluation of GMs must be done on video recordings, may it be prenatal or postnatal. These must be evaluated with “gestalt perception,” which could be described as overall impression of GMs with standardized procedure. It is important to recognize, document, and classify the movement pattern and then their complexity, variability, and fluency.22 These can be classified as normal-optimal, normal-suboptimal, mildly abnormal, and definitely abnormal.5,11 Quality of neurological movement is more important than the quantity. They can better predict neurodevelopmental outcome than classical neurologic examination alone.37

Why do Fetuses of Diabetic Mothers have Higher Risk of Neurological Derangements?

Gestational diabetes mellitus carries with it multiple risk factors for the developing fetus, and each has independent effects on neurodevelopment that may impact mnemonic behavior.38 These risk factors are: (1) Chronic hypoxia,39 (2) hyperglycemia/reactive hypoglycemia, and (3) iron deficiency.40 Based on the animal models, these factors selectively affect regions of the fetal brain that are involved in explicit memory (e.g., the hippocampus).38,41-43

Women with diabetic vascular disease have the highest malformation rates, leading to the belief that vascular disease and hypoxia are teratogenic.43 Maternal ketonuria in diabetic mothers is associated with reduced intelligence quotient in their infants,43-45 as ketones may interfere with normal development of fetal brain.43 Abnormal protein synthesis might also result from a lack of glucogenic amino acids or an overabundance of branched-chain amino acids, as is seen in poorly controlled diabetes.43,46

Jovanovic et al48 were able to study the pregnancy in diabetic women before the 10th week of gestation. Women with uncontrolled diabetes had estradiol, prolactin, and human chorionic gonadotropin levels below the range associated with normal pregnancy.43 When these risk factors co-occur, oxygen consumption of the fetus increases and causes fetal hypoxia,38,48 which can ultimately result in brain iron deficiency through shifting of available fetal iron away from the brain and into the expanding red cell mass.36,40 Prenatal hypoxia and hyperglycemia/reactive hypoglycemia cause poor behavioral and neurologic outcomes presenting as motor and cognitive deficits in humans49 and damage to memory areas, such as the cerebral cortex, striatum, and hippocampus in animal models.38,49 These factors together lead
to altered normal maturation of the behavioral states in fetuses with IUGR, maternal diabetes mellitus, or alcohol consumption.\textsuperscript{50}

**What to Observe for?**

**Assessment of Neurological Function**

Even when these movements were documented by 4D US, it was a very difficult task to classify these movements and based on these to judge the neurological developmental status of fetus. For the first time, a test was structured to assess the fetal CNS integrity and was named as Kurjak’s antenatal neurodevelopmental test (KANET).\textsuperscript{51} The KANET is the first test that is based on 4D US, with an original scoring system and has been standardized, so it can be implemented in everyday practice, overcoming the practical difficulties and covering the gaps of methods that were used in the past for the evaluation of fetal behavior.\textsuperscript{52,53} Improvement of 4D ultrasonography technology enabled introduction of KANET, which is a powerful tool in the assessment of fetal behavior and a guide to predict cerebral palsy.\textsuperscript{54} After experimental use for 10 years, a consensus was passed in Bucharest, concluding that KANET test can be used in everyday clinical practice for follow-up of fetuses at neurological risk with strong recommendations for strict and reliable multidisciplinary postnatal follow-up for at least 3 years. It has acceptable sensitivity, specificity, positive, and negative predictive value for neurodevelopmental anomalies.\textsuperscript{55}

The test is of more significance than the morphological studies of the brain. Analysis of the fetal behavior compared with morphological studies has concluded that fetal behavioral patterns are direct reflection of developmental and maturational processes of fetal CNS.\textsuperscript{56} The parameters that have been incorporated in the KANET test are isolated head anteflexion, overlapping cranial sutures, head circumference, isolated eye blinking, facial alterations, mouth opening (yawning or mouthing), isolated hand and leg movements and thumb position, and Gestalt perception of GMs.\textsuperscript{43,57}

Based on multicentric studies over several years, and on the theory of central pattern generators for GMs, certain fetal movements were chosen as parameters to assess neurological development.\textsuperscript{57,58} It is to be performed between 28 and 38 weeks, when fetus is awake. Fetus is observed for 15 to 20 minutes. If fetus is asleep, the scan is repeated after 30 minutes or after 14 to 16 hours. Each movement depending on its frequency is given a score of 0, 1, and 2 for nine parameters. A score of 0 to 5 is abnormal, a score of 6 to 13 is borderline and a score of more than 14 is normal.\textsuperscript{59} If the test is abnormal or borderline, it is to be repeated every 2 weeks, till delivery (Table 2).\textsuperscript{58}

**Table 2:** Score chart of fetal movements according to KANET\textsuperscript{62}

<table>
<thead>
<tr>
<th>Sign</th>
<th>Score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated head anteflexion</td>
<td>0</td>
<td>Abrupt</td>
</tr>
<tr>
<td>Cranial sutures and head circumference</td>
<td>Small range (0–3 times of movements)</td>
<td>Variable in full range, many alternation (&gt; 3 times of movements)</td>
</tr>
<tr>
<td>Isolated eye blinking</td>
<td>Not present</td>
<td>Not fluent (1–5 times of blinking)</td>
</tr>
<tr>
<td>Facial alteration (grimace or tongue expulsion)</td>
<td>Not present</td>
<td>Fluency (&gt; 5 times of alteration)</td>
</tr>
</tbody>
</table>

or

(Cont’d…)
Neurological Function in Fetus of a Diabetic Female

The results of a study by Edelberg et al.\textsuperscript{69} and Robertson and Dierker\textsuperscript{21} have shown that it is actually the changing maternal blood glucose level that affects the cyclicity and frequency of fetal motor activity, rather than persistently high blood glucose levels.\textsuperscript{60}

Visser et al.\textsuperscript{61} and Schulte et al.\textsuperscript{79} studied the neurological development of infants of diabetic mothers (IDMs) and found longer rapid eye movement sleep in newborn IDMs. There is evidence that it is the concurrent maternal blood glucose levels according to which the fetal movements may be affected in diabetic and nondiabetic pregnancies, but different studies have mixed results. Some studies have reported increased and some have shown decreased fetal movement with elevated blood glucose levels.\textsuperscript{21,62-67} Some have reported decreased fetal movement, \textsuperscript{68-70} and others have reported no effects.\textsuperscript{71-75} An increased rate of minor neurological dysfunction was found in a group of 32 children born to mothers with gestational diabetes, including some fine and gross motor deficits, compared with a group of control children.\textsuperscript{76,77}

Abnormalities in the fetal motor activity may consist of a delayed first emergence of specific movements, quantitative changes, and an abnormal quality of movements (i.e., changes in execution of movement patterns) and abnormal development of fetal behavioral states.\textsuperscript{49,55,56} Qualitative and quantitative assessment of fetal movements can be used for the recognition of cerebral dysfunctions and probably neuromuscular ailments. Alteration in the normal movement pattern in terms of frequency and strength is seen in IUGR, the pathophysiology of which is fetal hypoxia. In the fetuses of diabetic mothers, fetal hypoxia is the main pathophysiological factor and so similar changes in fetal movements can be observed. A study on diabetes-related influence on fetal motor activity revealed 1 to 2 weeks delayed appearance of almost all fetal behavioral patterns in the first 12 weeks of pregnancy except the fetal breathing movements.\textsuperscript{15,49}

Fetal breathing pattern is considered to be one of the important parameters of fetal wellbeing in late diabetic pregnancies. It is not affected by Braxton–Hicks contractions. This means that the fetal neural control of fetal breathing like movements differ in diabetic pregnancy than in normal.\textsuperscript{15,78}

<table>
<thead>
<tr>
<th>Sign</th>
<th>Score</th>
<th>Score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouth opening (yawning or mouthing)</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Isolated leg movement</td>
<td>Cramped</td>
<td>Poor repertoire or small in range (0–5 times of movement)</td>
<td>Variable in full range, many alternation (&gt; 5 times of movements)</td>
</tr>
<tr>
<td>Isolated hand movement</td>
<td>Cramped or abrupt</td>
<td>Poor repertoire or small in range (0–5 times of movement)</td>
<td>Variable in full range, many alternation (&gt; 5 times of movements)</td>
</tr>
<tr>
<td>or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand to face movements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fingers movements</td>
<td>Unilateral or bilateral clenched fist, (neurological thumb)</td>
<td>Cramped invariable finger movements</td>
<td>Smooth and complex, variable finger movements</td>
</tr>
<tr>
<td>Gestalt perception of GMs</td>
<td>Definitely abnormal</td>
<td>Borderline</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Total score
Cyclic Motility

Other aspects of fetal neurobehavioral organization are influenced by the altered metabolic environment. In spite of good clinical control of diabetes, the infants of these mothers have a risk of compromised neurological developmental outcome. Spontaneous fetal movement in the last trimester of human gestation is dominated by irregular oscillations on a scale of minutes [cyclic motility (CM)]. The movement pattern (increased and decreased movements in cyclicity in normal females) is steady but is altered in mothers with increased blood glucose levels. Early in the third trimester, changes in the rate of oscillation in fetal CM between the two periods of activity were inversely related to changes in maternal blood glucose levels. It is seen that relatively short-term fluctuation in maternal glucose metabolism, rather than chronically elevated blood glucose, is the effective perturbation of the intrinsic cyclic patterns in spontaneous fetal motor activity in diabetic pregnancies. The results revealed that fetal CM is more sensitive to fluctuations in maternal blood glucose levels during the early part of the third trimester of gestation than during the middle or end of the third trimester. The results suggest that disruption of the temporal organization of spontaneous fetal motor activity in diabetic pregnancies represents an acute response to fluctuations in the metabolic environment rather than alternation of CM development.

But according to other studies, the transient abnormality maternal glucose metabolism may affect fetal CM but does not cause any increased risk of poor general developmental outcome in children of diabetic mothers. The effects are similar in the fetuses of mothers with type I or gestational diabetes, and no difference when fetuses later classified as appropriate for large gestational age were considered separately (p > 0.05). The movement patterns are useful for early diagnosis of neurological disorders that become manifest in perinatal and postnatal period. The authors observed that a low KANET score is predictive of both intrauterine and neonatal death. The study demonstrated the evaluated and accepted KANET to detect and discriminate normal and abnormal fetal behavior in normal and in high-risk pregnancies. Except for higher incidence in the abnormal group, there was no marked difference in the different motor patterns studied.

Analysis of sick preterm infants revealed a “reduction of elegance” and fluency, variability, fluctuation in intensity, and speed instead of change in incidence of distinct motor patterns. Abo-Yaqoub et al showed in their study that the difference between the two groups were isolated head anteflexion (Fig. 3), isolated eye blinking, facial expressions, mouth movements (Fig. 4), finger movements (Fig. 5), isolated hand movements, hand-to-face movements (Fig. 6), and GMs (Fig. 7). For isolated leg movements (Fig. 8), and cranial sutures, the difference was not significant.

Athanasiadis et al applied KANET test to assess and compare fetal behavior and neurodevelopment in 152 pregnant women, classified as low-risk (n = 78) and high-risk (n = 74) pregnancies in the second and third trimester. The neurodevelopmental score was statistically significantly higher in the low-risk group compared with the high-risk group, though the score was higher in diabetes subgroup compared with the IUGR and the preeclampsia subgroup.

CONCLUSION

Inadequate glycemic control and vascular pathologies are the chief causes of neurological developmental inadequacies in fetuses of diabetic mothers. These can be assessed and predicted antenatally by KANET test.
Figs 3A to C: Anteflexion of the head of the fetal head (A), reverted back to the neutral position (B and C) again shows a slight anteflexion

Figs 4A to C: Series of images (A to C) show opening of the fetal mouth
Figs 5A to C: Movement of thumb noted as thumb fixed to fingers and flexed (A), thumb close to fingers but extended (B), and thumb separate from fingers (C)

Figs 6A to C: (A) Fetal face with eye open and hand close to the chin. (B) Hand raised to fetal eye and eye is hidden by the hand. (C) Supination of the hand and abduction of thumb and extension of fingers
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