

## Original Research Article

### **4D Ultrasound of Fetal Facial Expressions in Low and High-Risk Pregnancies as an Indicator of Fetal Neuro-Behavior in Last Trimester**

#### **Abstract**

**Background:** The evolution of four-dimensional (4D) ultrasound not only enabled a better visualization of fetal anatomy but also allowed the study of foetal behaviour in real time. The aim of this work was to evaluate fetal neuro-behavior in low and high-risk pregnancies through 4D ultrasound of fetal facial expressions in last trimester.

**Methods:** This prospective study enrolled 50 pregnant females at their last trimester with high-risk pregnancies and with intrauterine growth restriction. Pregnant females were divided into two equal groups, one was pregnant females with low-risk pregnancy and the other group was pregnant females with high-risk pregnancy. All patients were subjected to full history taking and 2D and 4D ultrasound examination

**Results:** Cranial sutures and head circumference, post-partum follow up and total KANET score were significantly different between two groups ( $P < 0.001$ ). Post-partum follow-up and total KANET score of high-risk subgroups were significantly different ( $P < 0.001$ ).

**Conclusions:** 4D ultrasound is considered now a great tool to evaluate foetal neuro-behaviour in low and high-risk pregnancies and to predict the neurological outcomes through foetal facial expressions in the last trimester.

**Keywords:** 4D Ultrasound, Foetal Facial Expressions, Low and High-Risk Pregnancies, Foetal Neuro-Behaviour.

## **Introduction:**

Assessment of fetal neurobehavior and detection of neurological impairment prenatally has been a great challenge in perinatal medicine. The evolution of four-dimensional (4D) ultrasound not only enabled a better visualization of fetal anatomy but also allowed the study of fetal behavior in real time. Kurjak Antenatal Neurodevelopmental Test (KANET) was developed for the assessment of fetal neurobehavior and the detection of neurological disorders, based on the assessment of the fetus by application of 4D ultrasound in the same way that a neonate is assessed postnatally. KANET is a method that has been applied for the past 10 years and studies show that it is a strong diagnostic tool and can be introduced into everyday clinical practice. We present all data from studies performed up to now on KANET, the following parameters are included in the KANET test: isolated head anteflexion, overlapping cranial sutures, head circumference, isolated eye blinking, facial alterations, mouth opening (yawning or mouthing) <sup>[1-3]</sup>.

The evaluation of fetal facial expressions is considered to reflect the normal neurological development of the fetus and may be a key to predicting fetal brain function and well-being. Facial movements are controlled by cranial nerves V and VII, which appear at around 10 and 11 weeks. Innervation of well-formed facial muscles begins at about 8 weeks of gestation, by 16 weeks all the muscles used in facial expressions are formed, and between the gestational ages of 24 and 36 weeks, facial adipose tissue is deposited and gradually builds up <sup>[4]</sup>.

There have been numerous studies on fetal facial expressions using conventional four-dimensional (4D) ultrasonography in the second and third trimesters of pregnancy. These studies raise the question as to whether facial expressions reliably represent a behavior or emotional state, or whether they constitute reflexive behavior by the fetus. How fetal facial movements become coordinated over time to form recognizable emotional expressions is not yet fully understood. If we can observe fetal facial expressions precisely, we can obtain new

and/or additional information to facilitate improved understanding of normal neurological development of the fetus and diagnosis of fetal brain impairment in utero <sup>[5-7]</sup>.

The aim of this work was to evaluate foetal neuro-behaviour in low and high-risk pregnancies through 4D ultrasound of fetal facial expressions in last trimester.

### **Patients and Methods:**

This prospective study enrolled 50 pregnant females at last trimester with high-risk pregnancies as Diabetes Mellites & hypertension and with intrauterine growth restriction.

An informed written consent was obtained from all patients. The study was done after approval from the Ethical Committee Tanta University Hospitals.

Exclusion criteria were Females with previous history of giving birth of neurologically impaired foetus and with familial history of neurological impairment. Pregnant females were divided according to the maternal background risk into two equal groups, one was pregnant females with low-risk pregnancy and the other group was pregnant females with high-risk pregnancy.

**All patients were subjected to** full history taking and 2D and 4D ultrasound examination.

**2D ultrasound examination:** All patients were initially scanned by 2D trans-abdominal probe using a TOSHIBA Aplio 500 ultrasound equipment with a convex abdominal transducer (3-5 MHz). The examination protocol included: basic examination of the head and face in three main axial planes with different measurements (BPD, HC, transcerebellar diameter & cisterna magna diameter) in addition to detailed neurosonographic examination in axial, sagittal and coronal planes. Examination of other body systems in addition to measurement of AC &FL.

**4D Ultrasound examination:** All pregnant women had 4D ultrasound examination in order to assess fetal behavior and neurodevelopment.

The examination protocol: starting examination by pressing 4D button. Setting the ROI by pressing SET or NEXT. Adjusting the ROI size by (a) pressing EDIT ROI (b) operating the trackball or (c) pressing the set button. Adjusting the flexible cut line by (a) pressing flexible cutline or (b) operating the trackball. Pressing 4D button or 4D live in the other menu on the touch panel. the image was enlarged to at least a third of the screen; the 4D volume box was adjusted to include the whole region of interest (face), placing the upper reference line of the volume box close to the most anterior parietal bone & placing the cut line of the volume box in the amniotic fluid, in the axial view starting at the level used to measure the biparital diameter at angle of 60 in late pregnancy. Then the multiplanar mode was used to examine the brain in the three orthogonal planes in some cases.

Adjusting the image, using different 4D options: when 4D mode was started, the 3D image for the area within the ROI and the planar images for the ROI were displayed. Changing the display layout by pressing the layout button sets the 4- layout frame (MPR). Pressing the dual button sets the 2-frame layout (2D image + 4D image). Pressing the single button sets the single frame-layout (4D image). Rotate the M button to rotate the image around the X axis. Rotate the PW button to rotate the image around the Y axis. Rotate the CDI button to rotate the image around the Z axis. Zooming the 4D image: Rotate the depth / zoom button. Cutting out the undesired portion of the 4D image: Setting the cut out start position using the trackball and operating the trackball. Rotating 4D image 90 degree in the clockwise direction through the rotate option in the touch panel. Storing the 4D data (volume data) by Pressing Raw Store button on the main panel. Storing the 4D image (a) the dynamic image by pressing clip store button (b) the still image by pressing the still store button. Termination of the examination by choosing QUIT from 4D menu or pressing the 2D button. Finally, observation of the stored images for previous examination in 4D mode by pressing patient browser button, selecting main menu, selecting 4D data then selecting view option from the

touch screen. Only images with an acceptable quality of the face were included in the study that allowed visualization of the mouth and eyes.

### Statistical analysis

All the data were entered into Excel sheet Microsoft Office Excel-2007 and analyzed statistically using SPSS Statistical Software (version 20.0.0: IBM Corp: Armonk, NY) and XL-STAT (Addinsoft, NY, USA). All the outcome variables, i.e., quantitative data, were summarized in the form of mean  $\pm$  standard deviation. Chi-square test was used for categorical variables, to compare between different groups. Sensitivity is the capacity of the test to correctly identify diseased individuals in a population “true positive”. The greater the sensitivity, the smaller the number of unidentified cases “false negatives”. To calculate it, divide TP by (TP+FN). Specificity is the capacity of the test to correctly exclude individuals who are free of the disease “true negatives”. The greater the specificity, the fewer “false positives” will be included. To calculate it, divide TN by (TN+FP). Accuracy: Rate of Agreement = (True positives + True negatives) / Total tested x 100. P value < 0.05 was considered significant.

### Results:

IUGR, hypertension and diabetes mellitus were significantly higher in high-risk group compared to low-risk group (P< 0.001).Table 1

**Table 1: Distribution of all cases, maternal age, and gestational age**

Subgroups	Group		Chi-Square	
	Low risk (n = 25)	High risk (n = 25)	X <sup>2</sup>	P-value
Low risk	25(100)	0(0.00)	50.000	<0.001*
IUGR	0(0.00)	8(32)		
Hypertension	0(0.00)	9(36)		
Diabetes Miletus	0(0.00)	8(32)		
Total	25(100)	25(100)		
Age (Years)			28.880 $\pm$ 3.160	
Gestational age (Weeks)			31.740 $\pm$ 1.688	
Total score			10.120 $\pm$ 2.616	

Data are presented as mean  $\pm$  SD or frequency (%). \*: significant P value, IUGR: Intrauterine growth restriction

Hand to head movement, mouthing & yawing and fascial alteration were significantly different between two groups ( $P < 0.001$ ,  $P = 0.001$ ,  $P = 0.003$ ) respectively. Table 2

**Table 2: Hand to head movement, mouthing & yawing and fascial alteration demographic data**

Hand to head movement	Group		Chi-Square	
	Low risk	High risk	X <sup>2</sup>	P-value
Not noted	0(0.00)	2(8)	23.529	<0.001*
2-3 times	0(0.00)	1(4)		
3 times	0(0.00)	1(4)		
4 times	0(0.00)	1(4)		
3-5 times	0(0.00)	11(44)		
More than times 5	25(100)	9(36)		
Total	25(100)	25(100)		
<b>Mouthing Yawing</b>				
2 times	0(0.00)	1(4)	17.568	0.001*
3 times	0(0.00)	1(4)		
3-4 times	0(0.00)	1(4)		
3-5 times	0(0.00)	10(40)		
More than times 5	25(100)	12(48)		
Total	25(100)	25(100)		
<b>Fascial alteration (Grimacing &amp; tongue expulsion)</b>				
3 times	0(0.00)	6(24)	14.009	0.003*
3-4 times	0(0.00)	1(4)		
3-5 times	6(24)	11(44)		
More than times 5	19(76)	7(28)		
Total	25(100)	25(100)		

Data are presented as frequency (%). \*: significant P value, X<sup>2</sup>: Chi-Square test.

Isolated eye blinking, head ante-flexion and leg movement were significantly different between two groups ( $P = 0.006$ ,  $P < 0.001$ ,  $P < 0.001$ ) respectively. Table 3

**Table 3: Isolated eye blinking, head ante-flexion and leg movement in low and high-risk pregnancy demographic data**

Isolated eye Blinking	Group		Chi-Square	
	Low risk	High risk	X <sup>2</sup>	P-value
Not noted	4(16)	11(44)	14.433	0.006*,
Once	13(52)	11(44)		
1-2 times	0(0.00)	3(12)		
3-5 times	1(4)	0(0.00)		
More than times 5	2(8)	0(0.00)		
Total	25(100)	25(100)		
<b>Isolated head ante-flexion</b>				
Not noted	0(0.00)	1(4)	34.308	<0.001*
3 times	1(4)	12(48)		
3-4 times	6(24)	0(0.00)		
4 times	7(28)	0(0.00)		
3-5 times	4(16)	12(48)		

<b>More than times 5</b>	7(28)	0(0.00)		
<b>Total</b>	25(100)	25(100)		
<b>Isolated leg movement</b>				
<b>2-3 times</b>	0(0.00)	1(4)	32.527	<0.001*
<b>3 times</b>	0(0.00)	7(28)		
<b>3-4 times</b>	0(0.00)	2(8)		
	2(8)	12(48)		
<b>More than times 5</b>	23(92)	3(12)		
<b>Total</b>	25(100)	25(100)		

Data are presented as frequency (%). \*: significant P value, X<sup>2</sup>: Chi-Square test.

Cranial sutures and head circumference, post-partum follow up and total KANET score were significantly different between two groups (P<0.001). Table 4

**Table 4: Cranial sutures and head circumference demographic data, post-partum follow-up of the cases and total KANET score of low and high-risk groups**

Cranial sutures and head circumference	Group		Chi-Square	
	Low risk	High risk	X <sup>2</sup>	P-value
<b>Overlapping of cranial sutures with HC Less than normal age</b>	0(0.00)	1(4)	28.125	<0.001*
<b>Normal cranial sutures with HC Less than normal age</b>	0(0.00)	9(36)		
<b>Normal cranial sutures with HC more than normal age</b>	0(0.00)	8(32)		
<b>Normal</b>	25(100)	7(28)		
<b>Total</b>	25(100)	25(100)		
<b>Post-partum follow-up of the cases</b>				
<b>Normal</b>	23(92)	5(20)	26.460	<0.001*
<b>NICU</b>	2(8)	16(64)		
<b>Died</b>	0(0.00)	4(16)		
<b>Total</b>	25(100)	25(100)		
<b>Total KANET score</b>				
<b>Normal</b>	23(92)	4(16)	29.170	<0.001*
<b>Abnormal</b>	0(0.00)	3(12)		
<b>Borderline</b>	2(8)	18(72)		
<b>Total</b>	25(100)	25(100)		

Data are presented as frequency (%). \*: significant P value, KANET: Kurjak Antenatal Neurodevelopmental Test, NICU: new-born intensive care unit, HC: head circumference

post-partum follow-up and total KANET score of high-risk subgroups were significantly different (P<0.001). Table 5

**Table 5: post-partum follow-up and total KANET score of high-risk subgroups**

Post-partum follow-up	Subgroups			Chi-Square	
	IUGR	Hypertension	Diabetes Miletus	X <sup>2</sup>	P-value
<b>Normal</b>	2(25)	0(0.00)	3(37.50)	33.667	<0.001*
<b>NICU</b>	5(62.5)	6(66.67)	5(62.5)		
<b>Died</b>	1(12.5)	3(33.33)	0(0.00)		

<b>Total</b>	8(100)	9(100)	8(100)		
<b>Total KANET score</b>					
<b>Normal</b>	2(25)	1(11.11)	1(12.5)	33.564	<0.001*
<b>Abnormal</b>	1(12.5)	2(22.22)	0(0.00)		
<b>Borderline</b>	5(62.5)	6(66.67)	7(87.50)		
<b>Total</b>	8(100)	9(100)	8(100)		

Data are presented as frequency (%). \*: significant P value, KANET: Kurjak Antenatal Neurodevelopmental Test, NICU: new-born intensive care unit, X<sup>2</sup>: Chi-Square test, IUGR: Intrauterine growth restriction

Total KANET score of low and high-risk groups was significantly lower in high risk compared to low-risk groups (P<0.001). Table 6

**Table 6: Total KANET score of low and high-risk groups, and high-risk subgroups**

	Group		T-Test	
	Low risk	High risk	t	P-value
<b>Total KANET score</b>	12.280±1.242	7.960±1.645	10.478	<0.001*
<b>High risk subgroups</b>				
<b>Low risk</b>	12.280±1.242		35.800	<0.001*
<b>IUGR</b>	8.000±1.852			
<b>Hypertension</b>	7.667±2.000			
<b>Diabetes Miletus</b>	8.250±1.035			

Data are presented as mean± SD, \*: significant P value, KANET: Kurjak Antenatal Neurodevelopmental Test, IUGR: Intrauterine growth restriction.

## Discussion

The 4D ultrasound improves the evaluation not only of the anatomical structures but also functional evaluation using multi-planner approach. In addition, the anatomical details can be reformatted using tomographic techniques and surface analysis of minor defects and can be performed also using high-definition technique -live (HD-Live) rendering technique [8].

In our study scores from antenatal KANET were compared between low- and high-risk groups, and showed differences between them, for eight out of the 10 parameters these included: head anteflexion, eye blinking, facial expressions grimacing, tongue expulsion, mouth movement such as yawning, jawing, swallowing, isolated hand movements, hand to face movements, fist and finger movements with no significant difference in isolated head ante flexion, cranial sutures and head circumference as in study done by Talic et al., [9]. The comparison of the two tests revealed positive correlation between them, proving that the neonatal exam (ATNAT) was a satisfactory confirmation of the prenatal ultrasound

examination (KANET), stating that KANET could offer useful information about the neurological status of the fetus and be applied in clinical practice <sup>[10]</sup>.

In our study all parameters of KANET were compared between high- and low-risk pregnancies and noticed important differences in fetal behavior between them. For pathological KANET score all parameters were significantly different however, Neto Raul <sup>[11]</sup> who compared all parameters of KANET between high- and low-risk pregnancies and noticed important differences in fetal behavior between them.

In our study all cases were the same race with no difference between in them in all parameters some studies for example Hanaoka et al. <sup>[12]</sup> also compared the findings of KANET between Caucasian and Asian populations. Total KANET score was normal in both populations, but there was a difference noted in total KANET scores between these two populations. When individual KANET parameters were compared, significant differences were observed in four fetal movements (isolated head anteflexion, isolated eye blinking, facial alteration or mouth opening, and isolated leg movement) <sup>[13]</sup>.

Mihaela Grigore et al., <sup>[14]</sup> described different patterns in fetal mouthing movements. They are represented by neutral mouth movements with a decreasing frequency with advancing gestation and lateralized mouth movements, which increase in frequency with advancing gestation.

Blinking represents a reflex response and is an important parameter for fetal brain functional development, easily observed with 4D US, in contrary to our study where eye blinking was hardly noted in high-risk pregnancy. It is regulated by the dopamine system and the increased rate of eye blinking along the pregnancy might be a parameter of the central dopamine system <sup>[15]</sup>.

In current study, yawning is considered highly significant as it compared between the previously mentioned two groups, usually yawning during pregnancy experiences a change in

frequency that indicates maturation of the brain. The frequency of yawning decreases after 28 weeks of gestation <sup>[16]</sup>.

All our cases were non-smoker with great difference in their score however Suzanne Froggatt et al., <sup>[17]</sup> compared facial expression of fetus from smokers versus non-smokers women. It appears that fetuses of mothers who smoked displayed higher rates of mouthing movements compared with those of nonsmokers. Fetuses suffering from stress display higher frequencies of facial expressions compared with non-stressed fetuses.

As in our study Mihaela Grigore et al., <sup>[14]</sup> observed that fetuses in primiparas showed a higher rate of eye blinking than those in multiparas. Because, according to these authors primiparas had a higher state of relaxation than multiparas this study of facial expressions suggests that that relaxation might promote fetal brain maturation, especially the central dopamine system, which regulates blinking.

Aida Salihagić Kadić et al., <sup>[18]</sup> study neonates were divided into three groups: normal, mildly, or moderately abnormal and abnormal and this led to the formation of the first KANET scoring system: 14–20 (normal), 5–13 (mildly or moderately abnormal) and 0–5 (abnormal). Following this preliminary study many others applied KANET and assessed its usefulness for the detection of neurological impairment during in utero life, in our study were divided into 3 groups normal (10-16 ), borderline (6-9) and abnormal (0-5) <sup>[19]</sup>.

In current study with 25 high-risk pregnancies identified 21 fetuses at neurological risk (3 cases with abnormal score and 18 case borderline) with 4 fetus died, one died in utero and 3 fetuses died after delivery and period in NICU while Asim Kurjak et al., [Kurjak, 2021 #23] in a study included 288 high-risk pregnancies identified 32 fetuses at neurological risk (seven cases with abnormal score and 25 with borderline). There were also 11 cases with abnormal KANET, of which six fetuses died in utero and five were terminated.

In current study the majority of normal KANET scores derived from the low-risk population about (92%) and only (8%) were borderline, while the majority of cases with borderline derived from the high-risk group (72%) and only (16%) were normal and only high-risk patient had abnormal score about (12%), Vladareanu et al., <sup>[20]</sup> also noted the same like our study. The authors concluded that KANET can be useful for the detection of neurological impairment that such a problem could become obvious during the antenatal or postnatal period.

Asim Kurjak and Panos Antsaklis <sup>[21]</sup> noted the same like our study that only high-risk patients showed abnormal scores, while comparing the two groups they noticed that 80.6% of high-risk patients had borderline results while 85.3% of low-risk patients were normal, both being statistically significant. For the 19 abnormal KANET results (score 0–5), five were related to pregnancy condition (preeclampsia, threatened preterm labor and drug abuse) and 14 were related to fetal condition (trisomy 13, 18 and 21 and IUGR). In our study for the 3 abnormal KANET results (score 0-5), two were related to pregnancy condition (preeclampsia) and one case related to fetal condition (IUGR).

Post-natal follow up of all fetuses especially with high-risk mothers and with abnormal KANET, four of them had confirmed pathological ATNAT score. Asim Kurjak et al. <sup>[22]</sup>, study also neonates with abnormal KANET were followed up post nately and three had confirmed pathological ATNAT score as in our study were three cases had confirmed pathological ATNAT score <sup>(88)</sup>. From the 20 cases diagnosed with borderline KANET result, 17 neonates showed a borderline ATNAT score and were followed up, while the three remaining cases showed normal ATNAT result.

## **Conclusions:**

4D ultrasound is considered now a great tool to evaluate fetal neuro-behavior in low and high-risk pregnancies and to predict the neurological outcomes through fetal facial expressions in the last trimester.

#### **COMPETING INTERESTS DISCLAIMER:**

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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