J. Perinat. Med. 41 (2013) 107–114 • Copyright © by Walter de Gruyter • Berlin • Boston. DOI 10.1515/jpm-2012-0018

Comparison between antenatal neurodevelopmental test and fetal Doppler in the assessment of fetal well being

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Abstract

Aims: The primary aim of this study was to compare circulatory changes in the fetal brain under certain pathological conditions with alterations in fetal behavior.
Patients and methods: A prospective longitudinal cohort study on fetal behavior of fetuses from singleton pregnancies between the 28th and 38th gestational week in the period from March 2009 to October 2011 was undertaken. There were 596 fetuses in the high-risk group and 273 fetuses in the low-risk group. Elevated umbilical artery Doppler pulsatility index and reduced middle cerebral artery pulsatility index obtained in the absence of fetal movements were considered abnormal. The Kurjak Antenatal Neurodevelopmental Test (KANET) was used to assess fetal behavior.
Results: Statistically significant differences in the distribution of normal, abnormal, and borderline KANET scores between low-risk and high-risk groups were found. Furthermore, 596 fetuses from the high-risk group were subdivided into subgroups according to the risk factor. The largest proportion of abnormal KANET scores (23.9%) was in the subgroup of fetuses whose mothers had an offspring diagnosed with cerebral palsy (23.9%), followed by the proportion of borderline KANET scores in the subgroup of fetuses from febrile mothers (12.7%). Fetal behavior was significantly different between the normal group and the following subgroups of fetuses: fetal growth restriction (FGR), gestational diabetes mellitus, threatened preterm birth, antepartal hemorrhage, maternal fever, sibling with cerebral palsy, and polyhydramnios.
Conclusions: A new clinical application of the KANET test in early identification of fetuses at risk for adverse neurological outcome was demonstrated.

Keywords: Fetal behavior; fetal Doppler; high-risk pregnancies.

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Introduction

Fetal behavior reflects developmental and maturational processes within the fetal central nervous system which was encouraging to use changes in fetal behavior for early diagnosis of neurological impairment [26]. Previous studies clearly showed significant differences in fetal behavior, in at risk- vs. normal pregnancies [1, 39]. Several pathological processes are involved in triggering the process which leads to brain injury and results in alterations of fetal behavior. Fetal hypoxia is one of the underlying mechanisms causing fetal brain impairment. Disorders of preplacental, uteroplacental or postplacental vasculature can result in insufficient nutrient- and oxygen supply for the fetus, accompanied by fetal hemodynamic changes ranging from adaptation to decompensation [3, 17, 33]. The redistribution of fetal blood flow, known as "brain sparing effect" is an adaptive mechanism to preserve sufficient supply for vital organs, such as brain, heart, and adrenal glands, which appears when fetal pO_2 drops to a critical level [33]. These circulatory changes related to fetal adaptation of catecholamine and cortisol levels to hypoxia can be demonstrated by Doppler ultrasound [17, 33]. Measuring umbilical artery and middle cerebral artery velocity waveforms by means of pulsed Doppler is widely used in obstetrics as a non-invasive method for the evaluation of fetoplacental circulation and blood flow in the fetal brain [11, 13, 33]. It is still unclear whether the relative preference of fetal brain perfusion in comparison with other fetal organs enables optimal neurodevelopment, or it should be already considered as an ominous sign of fetal brain damage [11, 13, 17, 18, 33]. Cerebral palsy (CP) is an umbrella term describing brain damage resulting in disorders of the tone, posture, and movements with multifactorial etiology [15]. It is a non-progressive disorder, but symptoms may change with brain maturation. The prevalence of CP is 1.5–2.5 per 1000 live births and has remained stable for the past 50 years [15]. It is now generally recognized that CP develops most frequently

after brain injury occurring *in utero,* caused by a variety of conditions, such as intrauterine infections, metabolic and genetic disorders, or congenital malformations [2].

The primary aim of this study was to compare circulatory changes in the fetal brain under certain pathological conditions with alterations in fetal behavior. The secondary goal was to look for new arguments proving the hypothesis that the brain sparing effect is not just a protective mechanism for neurodevelopmental processes in the fetal brain. To assess fetal behavior, we used a new neurobehavioral test, the Kurjak Antenatal Neurodevelopmental Test (KANET), to characterize the motor performance of the fetuses in low- and high-risk pregnancies in relation to fetal hemodynamic changes assessed by Doppler. The test and the first reports on its clinical value are described in detail elsewhere [21].

Methods

Patients

A prospective longitudinal cohort study on fetal behavior of fetuses from singleton pregnancies between the 28th and 38th gestational week (GW) in the period from March 2009 to October 2011 was undertaken. The gestational age (GA) was calculated using Naegele's rule (first day of the last menstrual period) and confirmed by ultrasound in the first or in the early second trimester. The study was approved by the local ethical committee. Participants, mostly illiterate, provided verbal informed consent prior to inclusion in the study. Pregnant women were divided into low- and high-risk groups. Inclusion criteria for the high-risk group are displayed in Table 1.

There were 596 fetuses in the high-risk group and 273 fetuses in the low-risk group. Fetuses from multiple pregnancies and those with detectable structural abnormalities were excluded from the study. All mothers were non-smokers, neither drug nor alcohol abusers.

Fetal assessment

The protocol was part of the larger study on fetal behavior in which data were collected during monthly check-ups beginning from the 28th GW. The GA of the fetuses at check-up time ranged from 28 to 36 weeks of gestation in the whole population, with a mean GA and standard deviation of 32±1.2 weeks in the high-risk group and 32±1.5 weeks in the low-risk group. Visits were scheduled between 14:00 and 16:00 h. Women were asked to refrain from eating 2 h before assessment. The first part of the assessment consisted of a two-dimensional ultrasound examination (2D US) for the evaluation of fetal position, growth, and anatomy followed by the estimation of fetal circulation. Elevated umbilical artery Doppler pulsatility index (UA PI) >2 standard deviations above the mean for GA and reduced middle cerebral artery pulsatility (MCA PI) index <2 standard deviations below the mean for GA, obtained in the absence of fetal movements were considered abnormal. The UA PI was measured in a free-floating loop of the umbilical cord. Measurements of the MCA PI were performed with color Doppler visualization of the circle of Willis in the fetal brain. Doppler studies were followed by the assessment of fetal behavior applying the KANET test using a four-dimensional ultrasound (4D US). The examinations were performed by experienced operators using the MEDISON 8X (Medison America Inc., CA, USA) with trans-abdominal 5 MHz transducer or the Voluson 730 pro with RAB 4 3D/4D probe (GE Healthcare, UK). The duration of examinations was up to 20 min for the KANET and <1 min for Doppler investigation. The exposure time per patient was always on the investigator's mind and usually the average KANET assessment time did not exceed 10 min. All parameters of the KANET scoring system were evaluated quantitatively and qualitatively, assigning to each parameter scores from 0 to 2. Scores from all parameters were summarized forming a total KANET score, including some modifications as described recently by our group [36].

Table 1 Inclusion criteria for the high-risk group.

Maternal conditions	Diabetes mellitus type I or II, Hypertension in pregnancy Maternal fever, Previous offspring with CP
Pregnancy-related conditions	Gestational diabetes, Rh immunization, Antepartum hemorrhage Threatened preterm birth
Fetal conditions	Fetal growth restriction

Statistical analysis

Statistical analysis was performed to answer the following questions:

- the distribution of fetuses assigned to different KANET groups,
- the comparison of KANET scores between investigated (high-risk) and control group of fetuses,
- the comparison of KANET scores within the subgroups of high-risk group, with normal fetuses,
- the distribution of normal and abnormal MCA PI within subgroups of the high-risk group of fetuses,
- the distribution of KANET scores in each subgroup of the high-risk group in relation to the MCA PI.

The contingency table test, χ^2-test, and logistic regression analysis were used in the statistical analysis performed by application of PAST version 2.00 (http://palaeo-electronica.org/2001_1/past/issue1_01.htm) and Kyplot version 4 (http://www.kyenslab.com/en/). A P-value ≤0.05 was considered statistically significant.

Results

The distribution of normal, borderline, and abnormal KANET scores in the low-risk group and in the high-risk group of fetuses is displayed in Table 2.

The contingency table test and χ^2-test revealed statistically significant differences in the distribution of

Table 2 The distribution of KANET scores in low- and high-risk groups of fetuses.

Group	n	KANET scores			P-value
		Normal n (%)	Borderline n (%)	Abnormal n (%)	
Low-risk	273	251 (91.9)	20 (7.3)	2 (0.7)	0.0016
High-risk	596	432 (72.5)	134 (22.5)	30 (5.0)	
Total	869	683	154	32	

n=number of examinees.

Table 3 The distribution of fetuses from the subgroups of high-risk pregnancies according to the KANET scores and comparison of KANET scores from the subgroups.

Subgroup of fetuses	n	KANET scores			P-value
		Normal n (%)	Borderline n (%)	Abnormal n (%)	
PIH	150	130 (86.69)	16 (10.6)	4 (2.6) NS	0.2872
FGR	60	40 (66.6)	18 (30)	2 (3.3)	0.0001
GDM	51	37 (72.5)	14 (24.7)	0 (0)	0.0006
Threatened PB	102	79 (77.4)	18 (17.6)	5 (4.9)	0.0079
Antepartal hemorrhage	44	21 (47.7)	21 (47.4)	2 (4.5)	0.0001
Maternal fever	55	17 (30.9)	31 (56.6)	7 (12.7)	0.0001
Sibling with CP	21	8 (38.1)	8 (38.1)	5 (23.9)	0.0001
Rh immunization	89	83 (93.2)	5 (5.6)	1 (1.1) NS	0.6611
Polyhydramnios	10	8 (80)	1 (10)	1 (10)	0.0025
Total	582	423 (72.7)	132 (22.7)	27 (4.6)	

n=number of examinees, PIH=pregnancy-induced hypertension, FGR=fetal growth restriction, GDM=gestational diabetes mellitus, PB=preterm birth, CP=cerebral palsy, NS=not significant.

normal, abnormal, and borderline KANET scores between the low-risk and high-risk groups. Furthermore, 596 fetuses from the high-risk group were subdivided into subgroups according to the risk factor. Two fetuses were from pregnancies complicated by type I diabetes mellitus. One of them had normal and the other one had abnormal KANET scores. Twelve fetuses were from mothers with type II diabetes mellitus. Eight of them had normal, two borderline, and two abnormal KANET scores. The distribution of KANET scores in the remaining subgroups of fetuses is displayed in Table 3.

The largest proportion of abnormal KANET scores (23.9%) was in the subgroup of fetuses whose mothers had an offspring diagnosed with CP, followed by the proportion of borderline KANET scores in the subgroup of fetuses from febrile mothers (12.7%). The same subgroup of fetuses also showed the largest proportion of borderline KANET scores (56.6%), followed by fetuses from pregnancies complicated by antepartal hemorrhage (47.4%). Fetal behavior differs significantly between the normal group and the following subgroups of fetuses: fetal growth restriction (FGR), gestational diabetes mellitus (GDM), threatened preterm birth (PB), antepartal hemorrhage, maternal fever, sibling with CP, and polyhydramnios.

The distribution of normal and abnormal was expectedly uneven in different subgroups of fetuses from the high-risk group. One out of two fetuses from pregnancies complicated by type I diabetes mellitus had abnormal MCA PI. This fetus also showed abnormal KANET score. Two fetuses out of 12 from pregnancies complicated by type II diabetes mellitus had abnormal MCA PI. One of them had borderline and the other one abnormal KANET score.

There were no fetuses with abnormal MCA PI in the low-risk group. Expectedly, the largest proportion of abnormal MCA PI was in the subgroup of FGR fetuses (71.6%), followed by fetuses from pregnancies complicated by antepartal hemorrhage (34.1%). Furthermore, the distribution of normal, borderline, and abnormal scores in relation to the normal vs. abnormal MCA PI for each subgroup of fetuses was analyzed. One out of two fetuses from pregnancies complicated by type I diabetes mellitus had abnormal MCA PI and abnormal KANET score. Two fetuses out of 12 from pregnancies complicated by type II diabetes mellitus had abnormal MCA PI. One of them obtained borderline and the other one abnormal KANET score. The distribution of normal and abnormal MCA PI among other subgroups of high-risk group is given in Table 4. The distribution of KANET scores related to MCA PI in fetuses from pregnancies complicated by pregnancy-induced hypertension is given in Table 5.

Fetal behavior is significantly different in the subgroup of fetuses with abnormal MCA PI. The distribution of KANET scores in FGR fetuses with normal and abnormal MCA PI are shown in Table 6. Among FGR fetuses with abnormal MCA

Table 4 The distribution of normal and abnormal MCA PI in fetuses from the subgroups of the high-risk group.

Subgroup of fetuses	n	MCA PI[a]	
		Normal n (%)	Abnormal n (%)
PIH	150	106 (70.6)	44 (29.3)
FGR	60	17 (28.3)	43 (71.6)
GDM	51	51 (100)	0 (0)
Threatened PB	102	100 (98.1)	2 (1.9)
Antepartal hemorrhage(APH)	44	29 (65.9)	15 (34.1)
Maternal fever	55	54 (98.2)	1 (1.8)
Sibling with CP	21	21 (100)	0 (0)
Rh immunization	89	83 (93.3)	6 (6.7)
Polyhydramnios	10	9 (90)	1 (10)
Total	582	461 (80.8)	112 (19.2)

[a]In 9 out of 582 fetuses from the high-risk group the MCA PI was not determined.

n=number of examinees, MCA PI=middle cerebral artery pulsatility index, PIH=pregnancy-induced hypertension, FGR=fetal growth restriction, GDM=gestational diabetes mellitus, PB=preterm birth.

Table 5 The distribution of KANET scores related to MCA PI in fetuses from pregnancies complicated by pregnancy-induced hypertension.

MCA PI	n	KANET scores			P-value
		Normal n (%)	Borderline n (%)	Abnormal n (%)	
Normal	106	105 (99.06)	1 (9.4)	0 (0.0)	0.0001
Abnormal	44	25 (56.8)	15 (34.1)	4 (9.9)	
Total	150	130 (86.7)	16 (10.7)	4 (2.6)	

n=number of examinees, MCA PI=middle cerebral artery pulsatility index.

Table 6 The distribution of KANET scores related to MCA PI in FGR fetuses.

MCA PI	n	KANET scores			P-value
		Normal n (%)	Borderline n (%)	Abnormal n (%)	
Normal	17	13 (76.5)	4 (23.5)	0 (0)	0.0249
Abnormal	43	27 (62.5)	14 (32.5)	2 (4.6)	
Total	60	40 (66.7)	18 (30.0)	2 (3.3)	

n=number of examinees, MCA PI=middle cerebral artery pulsatility index.

PI, 4.6% had abnormal, and 32.5% had borderline KANET scores, which was statistically significant compared with FGR fetuses with normal MCA PI.

Table 7 shows a comparison of the KANET test in fetuses from threatened preterm labor with normal or abnormal MCA PI. There were two fetuses with abnormal MCA PI in the group complicated with threatened preterm labor with abnormal KANET scores, which was statistically significant, as shown in Table 7.

The distribution of KANET scores in fetuses from pregnancies complicated with antepartal bleeding who had abnormal or normal MCA PI is shown in Table 8. All fetuses from pregnancies complicated by antepartum hemorrhage with abnormal KANET score had abnormal MCA PI. Borderline KANET score was observed in 80% of fetuses with abnormal MCA PI vs. 31.1% of fetuses with normal MCA PI.

Table 7 The distribution of KANET scores related to MCA PI in fetuses from pregnancies complicated by threatened preterm birth.

MCA PI	n	KANET scores			P-value
		Normal n (%)	Borderline n (%)	Abnormal n (%)	
Normal	100	79 (79)	18 (18)	3 (3)	0.0017
Abnormal	2	0	0	2 (100)	
Total	102	79 (77.5)	18 (17.6)	5 (4.9)	

n=number of examinees, MCA PI=middle cerebral artery pulsatility index.

Table 8 The distribution of KANET scores related to MCA PI in fetuses from pregnancies complicated by antepartum hemorrhage.

MCA PI	n	KANET scores			P-value
		Normal n (%)	Borderline n (%)	Abnormal n (%)	
Normal	29	20 (68.9)	9 (31.1)	0 (0)	0.0001
Abnormal	15	1 (6.6)	12 (80)	2 (13.3)	
Total	44	21 (47.7)	21 (47.7)	2 (4.6)	

n=number of examinees, MCA PI=middle cerebral artery pulsatility index.

The distribution of KANET scores in fetuses whose mothers were febrile during pregnancy who had abnormal or normal MCA PI is shown in Table 9. Although it was only one fetus whose mother had fever during pregnancy with abnormal MCA PI and abnormal KANET score, the difference was statistically significant. More than half of the fetuses whose mothers have been febrile had borderline or abnormal KANET score.

The distribution of KANET scores in fetuses with Rh immunization related to MCA PI is shown in Table 10. Abnormal MCA PI was found in six fetuses of whom four had borderline KANET score, in one KANET was normal and in one abnormal. The difference was statistically significant.

Table 11 shows normal and abnormal MCA PI in relation to the KANET scores analyzed by logistic regression analysis. The results were statistically significant. Regarding the fetuses from pregnancies complicated with type I and type II diabetes mellitus and their MCA PI and KANET scores, the difference was not statistically significant due to a small sample size, which is the reason why these data are not shown in separate tables.

The group of fetuses from pregnancies complicated with GDM was higher, but there were no abnormal MCA PI detected in that group, whereas only in 14 (27.4%) out of 51 fetuses the KANET scores were borderline. This was the reason why these data were also not shown separately.

In 21 fetuses with siblings affected by CP abnormal MCA PI was not detected, whereas in five of them abnormal KANET scores were detected. There were 10 fetuses with polyhydramnios. In one of the fetuses abnormal MCA PI was

Table 9 The distribution of KANET scores related to MCA PI in fetuses from febrile mothers.

MCA PI	n	KANET scores			P-value
		Normal n (%)	Borderline n (%)	Abnormal n (%)	
Normal	54	17 (31.5)	31 (57.4)	6 (11.1)	0.0001
Abnormal	1	0 (0.0)	0 (0.0)	1 (100.0)	
Total	55	17 (30.9)	31 (56.4)	7 (12.7)	

n=number of examinees, MCA PI=middle cerebral artery pulsatility index.

Table 10 The distribution of KANET scores related to MCA PI in fetuses from pregnancies complicated with Rh immunization.

MCA PI	n	KANET scores			P-value
		Normal n (%)	Borderline n (%)	Abnormal n (%)	
Normal	83	82 (96.4)	1 (1.2)	0 (11.1)	0.0001
Abnormal	6	1 (16.6)	4 (66.7)	1 (16.6)	
Total	89	83 (93.3)	5 (5.6)	1 (1.1)	

n=number of examinees, MCA PI=middle cerebral artery pulsatility index.

noted with normal KANET score, whereas one fetus from that group with abnormal KANET had normal MCA PI.

The distribution of fetuses from high-risk pregnancies according to the uterine artery pulsatility index (UAPI) is shown in Table 12. UAPI has been abnormal only in the subgroups of fetuses from the pregnancies complicated with pregnancy induced hypertension, FGR, and antepartal hemorrhage.

The correlation of KANET scores and pathological UAPI in fetuses from the high-risk pregnancies complicated with pregnancy induced hypertension, FGR, and antepartal hemorrhage is shown in Tables 13–15. The correlation was statistically significant only for the FGR fetuses and fetuses from the pregnancies complicated with antepartal hemorrhage.

Discussion

According to scientific evidence reduced placental perfusion is a result of endovascular trophoblast invasion failure which normally occurs as early as 10–12 weeks, finishing around 20 weeks [8]. In normal pregnancies embryonic cytotrophoblast cells invade maternal decidua and myometrium finding their way into the endothelium and highly muscular tunica media of the maternal spiral arteries [24, 27]. As a result of this invasion, the maternal uterine spiral arteries are transformed from muscular arteries with elastic lamina into flaccid tubes with a vascular radius four times wider than before, turning the placental vascular bed into a low resistance flow area for both fetal and maternal arterial inflow [8, 24]. In pre-eclampsia, for example, which is often associated with FGR, cytotrophoblast

Table 11 The distribution of normal/abnormal MCA PI in relation to KANET scores.

KANET scores	n	MCA PI		P-value
		Normal n (%)	Abnormal n (%)	
Normal	432	378 (87.5)	54 (12.5)	0.0001
Borderline	134	87 (64.9)	47 (35.1)	
Abnormal	30	16 (53.2)	14 (37.8)	
Total	596	481	115	

n=number of examinees, MCA PI=middle cerebral artery pulsatility index.

Table 12 The distribution of fetuses from the subgroups of high-risk pregnancies according to the UAPI.

Subgroup of fetuses	n	UAPI	
		Normal n (%)	Abnormal n (%)
PIH	150	56 (37.3)	94 (62.7)
FGR	60	42 (70)	18 (30)
Antepartal hemorrhage	44	42 (95.5)	2 (4.5)
Fetuses from other high-risk subgroups of pregnancies	328	328 (100)	0 (0)
Total	582	468 (80.4)	114 (19.6)

n=number of examinees, PIH=pregnancy-induced hypertension, FGR=fetal growth restriction, UAPI=uterine artery pulsatility index.

cells infiltrate the decidua, but fail to penetrate the maternal myometrium [24, 29]. Mammalian placentation requires extensive angiogenesis for the establishment of a suitable vascular network to supply oxygen and nutrients to the fetus [24, 29]. A variety of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), placenta growth factor, and anti-angiogenic factors, such as soluble VEGF receptor Flt-1 and soluble endoglin are produced by the growing placenta [26]. The balance of these factors is important for normal placental vascular development, whereas an increased production of anti-angiogenic factors tilts this balance and promotes systemic endothelial dysfunction [8].

Fetal blood circulation

The distribution of the oxygen- and nutrient-rich blood within the fetus is regulated by three particular features of fetal circulation: ductus venosus (DV), foramen ovale (FO), and ductus arteriosus Botalli [6, 10]. There is high oxygen saturations and increased partial pressure of oxygen (pO_2) of the upper and relatively decreased pO_2 of the lower body [6, 10].

Ductus venosus A preferential increase in DV flow at the expense of hepatic flow under conditions of fetal hypoxemia will result in increase of fraction of oxygenated venous blood going straight through the FO into the left cardiac circuit, and thus increased oxygen delivery to the myocardium and the

Table 13 Correlation between KANET scores and UAPI in pregnancies with PIH.

UAPI	n	KANET scores			P-value
		Normal n (%)	Borderline n (%)	Abnormal n (%)	
Normal	56	52 (92.8)	3 (5.3)	1 (1.8)	0.0769
Abnormal	94	78 (82.9)	13 (13.9)	3 (3.2)	
Total	150	130 (86.7)	16 (10.7)	4 (2.6)	

n=number of examinees, UAPI=uterine artery pulsatility index, PIH=pregnancy-induced hypertension.

Table 14 Correlation between KANET scores and UAPI in pregnancies with FGR.

UA PI	n	KANET scores			P-value
		Normal n (%)	Borderline n (%)	Abnormal n (%)	
Normal	42	34 (80.9)	7 (16.6)	1 (2.3)	0.0001
Abnormal	18	6 (33.3)	11 (61.1)	1 (5.5)	
Total	60	40 (66.7)	18 (30.0)	2 (3.3)	

n=number of examinees, UAPI=uterine artery pulsatility index, FGR=fetal growth restriction.

Table 15 Correlation between KANET scores and UAPI in pregnancies with antepartal hemorrhage.

UAPI	n	KANET scores			P-value
		Normal n (%)	Borderline n (%)	Abnormal n (%)	
Normal	42	21 (50)	21 (50)	0 (0)	0.0001
Abnormal	2	0 (0)	0 (0)	2 (100)	
Total	44	21 (47.7)	21 (47.7)	2 (4.6)	

n=number of examinees, UAPI=uterine artery pulsatility index.

brain. If hypoxemia and redistribution is chronic, abdominal circumference will become disproportionally low due to reduced glycogen storage in the liver [3, 4, 14, 19].

Middle cerebral artery (MCA) MCA and anterior cerebral artery (ACA) can be visualized with color and power Doppler, as bilateral major lateral and rostral branches of the circle of Willis [10]. Clerici and Di Renzo reported in a study including 20 normal and 8 FGR fetuses lower pulsatility index (PI) in proximal and distal portion of the MCA during periods of fetal movements compared with states of fetal quiescence [4, 6]. This change in PI was pronounced in the distal MCA section. They could demonstrate that FGR fetuses had already exhausted their capabilities of reducing PI in both proximal and distal MCA and had no significant further reduction of resistance-to-flow during movement states [4, 6].

The fetus adapts to placental insufficiency by vasodilatation of the cerebral circulation, with preferential perfusion of the central nervous system (CNS), a coping strategy which is called "brain sparing effect" [7, 13, 33]. In the fetus, these adaptive changes can be demonstrated by Doppler ultrasound, as decreased PI in the cerebral arteries. The Doppler indicator of "brain sparing" is a raised ratio between the umbilical artery PI and the MCA PI, called the U/C ratio. The term "brain sparing" refers to relative protection of the brain, heart, and adrenals under conditions of chronic hypoxemia, through sacrifice of perfusion in liver, kidneys, intestine, integument, and extremities, but does not guarantee normal neurodevelopment after birth [33, 37]. In fact, recent findings demonstrate that in FGR fetuses "brain sparing" is a misleading expression because it could predict cognitive deficits at the age of 5 years [9, 12]. Recent studies suggest that the ACA may be a better predictor of adverse neurological outcome than the MCA [17]. A study investigating the multifactorial etiology of CP found a strong association between FGR and CP: FGR was found in 34% in a series of 213 children diagnosed with CP [37]. Recent advances in understanding CP and other neurodevelopmental disorders as a result of insults during the prenatal period are about to induce a paradigm shift in jurisdiction in unfavorable perinatal outcome [1].

Umbilical arteries (UAs) With advancing gestation, a typical increase in diastolic velocity could be demonstrated, beginning with absent end-diastolic flow in the first trimester, going to low resistance with high end-diastolic flow in the third trimester [17]. It has been clearly demonstrated that abnormal umbilical artery Doppler correlates with histological evidence of placental vascular pathology [22]. Growth restricted fetuses with pathological UA waveforms, such as absent or reversed end-diastolic flow are known to be at higher risk for adverse perinatal outcome than those growth restricted fetuses with normal flow profiles [4, 5].

Uterine arteries Similar to the umbilical arteries, their resistance- and pulsatility indices decrease towards term [42]. At term, the normal uterine blood flow reaches 600 mL/min. Abnormal flow patterns of the uterine arteries with increased PI, decreased diastolic flow, and diastolic notching indicate increased downstream resistance-to-flow [42].

We demonstrated abnormal PI in uterine arteries in 62.7% of fetuses from pregnancy induced hypertension, 30% of fetuses with FGR, and 4.5% of fetuses with antepartal hemorrhage (Table 12), which was in concordance with previous studies [4, 5]. According to a study by Pongrojpaw et al., in high-risk women, mid-trimester uterine artery Doppler waveform analysis cannot be used as a screening method in women at higher risk for the development of severe adverse outcome, such as pre-eclampsia and small for gestational age babies [25]. However, women with normal uterine artery Doppler results are unlikely to develop pre-eclampsia, FGR, and therefore do not necessarily need repeated Doppler ultrasound follow-up [25].

Fetal behavior

Human fetuses, and in continuation, newborn children up to the age of 4 months post-term, have distinct patterns of spontaneous, not externally triggered movements, called general movements (GMs) which are defined by Prechtl [28] as gross movements, involving the whole body and lasting from a few seconds to several minutes or longer. GMs can be described as a variable sequence of arm, leg, neck, and trunk movements, which begin gradually, increase in force and speed, and then slacken down again. Extension and flexion movements of arms and legs are mostly complex and variable due to integrated rotations and frequent minor changes of direction, which adds a fluent and elegant quality to the movements [28]. The nature of the recognizable temporal sequences of

GMs lies in the intrinsic properties of neurons which spontaneously begin to generate and propagate action potentials on their own, and this happens even more frequently as soon as they are interconnected [34].

Assessment of fetal behavior in different periods of gestation promises recognition and early diagnosis of abnormal brain development and various structural and functional CNS abnormalities [28, 35]. Assessing KANET in fetuses of the mothers with pregnancy induced hypertension who had abnormal PI in umbilical artery, the correlation between KANET scores and PI in umbilical artery was not statistically significant due to a small number of fetuses.

Since 2001, a growing number of papers on four-dimensional findings of fetal behavior have been published reflecting the great interest of the medical research community in fetal neurology. A landmark in the study of fetal movements is certainly the creation of KANET [21], as a result of longitudinal evaluation of typical fetal movements in all three trimesters, and as a review of the existing knowledge about links between abnormal fetal movements and functional and structural CNS abnormalities [15, 22, 23].

From an anthropological perspective, the energetically expensive *in utero* development of a large human brain is vitally depending on the human-specific extremely deep endovascular invasion of the trophoblast, in order to be successful [30, 31]. Hence, it is no surprise that the fetus uses "brain sparing" as one of the main coping strategies in order to direct oxygen and nutrient enriched placental venous return towards the brain, heart, and adrenals when exposed to utero-placental vascular insufficiency with the inevitable consequences of nutrient, supplement, and finally oxygen deficiency [30, 31].

Based on this, it is not surprising that adverse pregnancy conditions, such as gestosis, FGR, famine during pregnancy (protein-energy malnutrition), and severe chronic maternal stress or depression have been linked to altered fetal movement patterns, echogenicity changes of the fetal brain, to higher incidence of neurodevelopmental disorders in childhood, and to occurrence of autism, schizophrenia, and epilepsy in the adult [1, 3, 5, 9, 12, 16, 32, 40, 41].

The question arising now is: can KANET function as a "diagnostic window into fetal brain development" and already trace *in utero* borderline or abnormal fetal movement patterns in at-risk pregnancies complicated, for example, by preeclampsia, FGR, GDM, and thus provide more information about the neurological prognosis in fetuses? A recent prospective longitudinal cohort study evaluating four-dimensional sonography in the assessment of fetal behavior in high-risk pregnancies [39] applied KANET in 620 singleton pregnancies between 26 and 38 weeks of gestation, in a 1-year period from January to December 2007. The study showed that KANET was able to identify borderline and abnormal fetal behavior in high-risk patient groups, such as gestosis and FGR [39]. These results support growing evidence that many neurological disorders originate from intrauterine rather than peri- or postnatal periods. This makes a great difference for the obstetrician with regard to CP [38], and is still one of the main causes of medico-legal conflicts, and might open new perspectives of prevention and therapy of neurodevelopmental disorders [1, 20].

Conclusions

This is the first study to examine the alteration in fetal behavior, measured by the KANET test in relation to fetal circulatory changes in umbilical and brain arteries, in different categories of at-risk pregnancies. We found significant differences in fetal behavior when circulatory changes in fetal brain were present. Circulatory changes were found as pathophysiologically expected in the group of FGR fetuses with abnormal fetal behavior under conditions of fetal hypoxia. This study, however, demonstrates that a substantial proportion of FGR fetuses with borderline or abnormal KANET scores still showed normal brain circulation when MCA PI was measured. This suggests that in the escalation of pathophysiological events *in utero*-placental insufficiency alterations of fetal behavior occur prior to "brain sparing". It appears as if fetal behavior changes before MCA adaptation mechanisms react to hypoxia. This may be a supporting argument in the discussion of the hypothesis that "brain sparing" is not an entirely protective mechanism for neurodevelopmental processes in the fetal brain, i.e., that brain damage is already signaled by altered fetal behavior. The data also suggest a new clinical application for the KANET test in early identification of fetuses at risk for adverse neurological outcome. Further research in this field may help in uncovering other factors (such as nutrient deficiency) causing alterations of fetal behavior and eventually brain injury, and to improve understanding of the pathogenesis of CP.

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The authors stated that there are no conflicts of interest regarding the publication of this article.

Received January 30, 2012. Revised February 13, 2012. Accepted February 16, 2012. Previously published online March 21, 2012.