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Relations between fetal brain-sparing circulation, oxytocin challenge test, mode of delivery and fetal outcome in growth-restricted term fetuses

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Running title: MCA Doppler flow velocimetry in management of IUGR

ABSTRACT

Objective: To elucidate the potential value of fetal middle cerebral artery Doppler velocimetry to identify brain-sparing flow in a surveillance program for suspected intrauterine growth restriction (IUGR).

Design: Prospective non-interventional observational study.

Setting: Skåne University Hospital, Malmö, Sweden.

Sample: 126 single pregnancies suspected of IUGR at ≥36 gestational weeks.

Main outcome measures: Positive/negative oxytocin challenge test (OCT), cesarean/vaginal delivery.

Methods: The pregnancies were managed with ultrasound fetometry, uterine and umbilical artery Doppler flow velocimetry, nonstress test, and an OCT to decide the optimal time and mode of delivery. Cases with a positive OCT were promptly delivered by cesarean section, whereas negative cases were allowed a trial of labor. Middle cerebral artery Doppler flow velocimetry results were blinded to the managing obstetricians. Brain-sparing flow was defined as a middle cerebral artery-to-umbilical artery pulsatility index ratio of <1.08. Non-parametric statistics with a $p<0.05$ were used, and Cohen's kappa coefficient was calculated for congruence of brain-sparing flow with OCT and mode of delivery, respectively.

Results: The positive predictive value and sensitivity figures of brain-sparing flow to indicate a positive OCT and cesarean delivery were 33-63%. The inter-rater reliability of brain-sparing flow vs. positive OCT showed a kappa coefficient of 0.19, and brain-sparing flow vs. cesarean section among OCT negative cases a kappa coefficient of 0.23.

Conclusion: Fetal brain-sparing flow is a poor predictor of a positive oxytocin challenge test, and of cesarean section in oxytocin challenge test negative cases.

Key words: brain-sparing; Doppler; IUGR; middle cerebral artery; oxytocin challenge test

ABBREVIATIONS

BSF	Brain-sparing flow
CI	Confidence interval
CS	Cesarean section
IUGR	Intrauterine growth restriction
MCA	Middle cerebral artery
NICU	Neonatal intensive care unit
OCT	Oxytocin challenge test
PI	Pulsatility index
SD	Standard deviation
UA	Umbilical artery

INTRODUCTION

A growth-restricted fetus must balance the reduced placental oxygen delivery with a lower tissue oxygen consumption. Eventually, chronic hypoxia develops with redistribution of blood flow to vital organs. Redistribution towards the brain, called brain-sparing flow (BSF), is a common feature in fetuses exposed to chronic hypoxia.

The clinical value of diagnosing BSF in fetuses with intrauterine growth restriction (IUGR) is controversial. Some studies support the value of diagnosing BSF in clinical management (1-4), whereas critics argue that the presence of BSF has a poor predictive value on perinatal outcome (5,6), and in the absence of BSF one never knows whether a transient BSF has first appeared (7).

Management programs for fetal surveillance in IUGR pregnancies adapt to local traditions and experience. At our obstetric unit, ultrasound fetometry, Doppler blood flow velocimetry, nonstress test and assessment of amniotic fluid volume are standard measures. Unless the nonstress test is pathological or the umbilical artery blood flow is severely affected, i.e. showing absent or reversed diastolic flow, the option is usually vaginal delivery. To optimize the decision on timing and mode of delivery in term IUGR pregnancies, we have systematically performed an oxytocin challenge test (OCT). Our experience with this tool is excellent (8).

We have used Doppler velocimetry with measurements of impedance in the middle cerebral artery (MCA) and other fetal vessels before and during the OCT in a scientific model to study fetal circulatory redistributions during provoked acute hypoxia (9,10). The results of MCA flow have never been used for clinical management in pregnancies complicated by IUGR, which gave us an opportunity to investigate the potential value of performing MCA Doppler flow velocimetry in addition to other tools for antenatal fetal surveillance in IUGR pregnancies.

MATERIAL AND METHODS

At the Skåne University Hospital in Malmö, Sweden, a consecutive series of 126 singleton pregnancies after 36 completed gestational weeks with suspected IUGR were managed according to a clinical protocol with repeated ultrasound examinations, Doppler blood flow velocimetries in the uterine and umbilical arteries, nonstress tests, assessments of the amniotic fluid volume, and OCT, as previously described (8). All pregnancies were dated at an early second trimester ultrasound examination and a second routine ultrasound scan was performed at 32-33 weeks for fetal growth estimation. Suspected IUGR was defined by ultrasound estimated fetal weight below the gestational age-adjusted mean value minus 2 SD (2.3rd percentile), or a fall of ≥10% weight deviation from the mean weight between two ultrasound examinations.

Women with no decisive indication to perform an elective cesarean section (CS) were included in the study. Women with an abnormal nonstress test or with absent or reversed end-diastolic flow in the umbilical artery were routinely delivered by CS and these women were not exposed to an OCT. As part of the clinical management protocol, the OCT was performed on the indication to take a decision on timing and mode of delivery. OCT negative cases were subsequently planned for either a prolongation of pregnancy or induction of labor, whereas OCT positive cases were promptly delivered by CS. Although false positive OCTs occasionally occur, it is our policy to deliver women with a positive OCT by CS.

In an experimental model to study uteroplacental and fetal dynamic circulatory changes during and between uterine contractions, we have in other published studies performed Doppler blood flow velocimetries in different uterine and fetal vessels simultaneous to electronic fetal heart rate monitoring during the OCT. These studies included recordings of MCA blood flow velocity waveforms, but only Doppler flow results from the uterine and umbilical arteries performed before the OCT were revealed for clinical management.

The blood flow measurements were performed with an Acuson Sequoia 512 real-time ultrasound scanner (Acuson, Mountain View, CA, USA) with an automatic step-less 2.5 to 6

MHz probe with pulsed and color flow Doppler options. The high-pass filter is automatically adjusted in this equipment. The mechanical index and thermal index were displayed and both indices were under 1 for the exposure to the Doppler output energy. The Doppler flow velocimetries were performed during fetal and uterine quiescence. Three consecutive flow velocity waveforms of optimal quality were used to calculate the pulsatility index (PI).

Flow velocity waveforms in the umbilical artery (UA) were recorded in a free floating loop of the middle part of the umbilical cord and the PI correlated to reference values (11).

By color Doppler imaging, the MCA was identified as a major lateral branch of the circle of Willis running anteriorly-laterally towards the lateral edge of the orbit on a transverse section of the fetal head at the level of the cerebral peduncles. Pulsations in the MCA on its course in the Sylvian fissure were identified and the pulse Doppler gate placed in the middle part of the vessel with an insonation angle close to 0°. BSF was defined as an MCA PI-to-UA PI ratio of <1.08 according to Gramellini *et al.* (12). Since not only a decrease of MCA PI but also an increase of UA PI cause a decrease of the MCA-to-UA PI ratio, a low MCA PI indicating BSF was also defined as being below the gestational age-adjusted mean value minus 2 SD according to Mari & Deter (1).

Primary outcome parameters were the result of the OCT and mode of delivery; secondary outcome parameters were Apgar score at 5 minutes, umbilical cord arterial and venous blood pH, and transfer to the neonatal intensive care unit (NICU). An Apgar score of <7 at 5 minutes, an umbilical cord arterial pH of <7.10 at birth and a venous pH of <7.15 were judged abnormal.

Statistical analyses

The chi-squared test and Fisher's exact test were used to compare categorical variables between groups, and the Mann-Whitney U test for comparison of continuous variables between groups. A two-tailed p-value of <0.05 was considered significant. The positive and negative predictive values, sensitivity, specificity, and Cohen's kappa coefficient were calculated from categorical variables in four-field tables. Cohen's kappa coefficient was used to correct for agreement occurring by chance. The kappa coefficient can reach a maximum value of 1.0, where values close to 1.0 indicate an almost perfect agreement between the test result and the clinical outcome; values <0.40 indicate a poor agreement, 0.40-0.59 fair agreement, 0.60-0.74 good agreement, and values of ≥0.75 excellent agreement. Statistics were performed with aid of StatView® (SAS Institute, Cary, NC, U.S.A.) and MedCalc® (MedCalc Software, Mariakerke, Belgium) computer software; Cohen's kappa coefficient with 95% confidence interval (CI) was calculated online with VassarStats' website for statistical computation (13).

The study was approved by the Research Ethics Committee at the Lund University Medical Faculty (LU 2009/222) and all participating women gave their informed consent.

RESULTS

A BSF was recorded in 27 of the 126 fetuses (21.4%). Table 1 shows demographic characteristics with statistical comparisons between the groups. A positive OCT, CS, lower gestational age, and lower birthweight were more common in the BSF group, but umbilical cord blood acidosis, low Apgar score and transfer to the NICU were not different. Among OCT positive women, 8/20 (40%) of fetuses showed BSF, and among OCT negative 19/106 (17.9%) (p= 0.058).

The congruence between BSF and the OCT result and mode of delivery is displayed in Table 2. Overall, the diagnostic statistics for BSF as a predictor of a positive OCT result and cesarean delivery showed a Cohen’s kappa coefficient between 0.19 and 0.26.

Corresponding to the analyses in Table 2 (where BSF was defined as an MCA-to-UA PI ratio < 1.08), statistics were performed also with a low MCA PI defined as PI <mean minus 2 SD (table not shown). A total of 12 fetuses (9.5%) then had a low MCA PI: two in the OCT positive group and 10 in the OCT negative group (Fisher’s test, p=1.0). The congruence statistics between presence/absence of a low MCA PI and positive/negative OCT showed a Cohen’s kappa coefficient of 0.007 (95% CI 0-0.33). For presence/absence of a low MCA PI vs. CS/vaginal delivery among OCT negative cases the statistics showed a kappa coefficient of 0.23 (95% CI 0-0.47).

DISCUSSION

The aim of this study was to assess the value of performing Doppler flow velocimetry in the MCA, i.e. whether the presence of BSF could predict the OCT result, and, in OCT negative women planned for vaginal delivery, the mode of delivery. This was done in an observational non-interventional way, with the MCA Doppler results concealed for the managing obstetricians. The presence of BSF and a positive OCT was then compared, and among OCT negative cases the presence of BSF and delivery by CS. Although vaginal delivery was significantly less common in the BSF group, the positive predictive value and sensitivity figures for a positive OCT result and cesarean delivery were poor (≤63%), and Cohen's kappa coefficient indicated a poor agreement between the phenomena (coefficients ≤0.26). Defining BSF as an MCA-to-UA PI ratio of <1.08, or MCA PI below the gestational age-adjusted mean value minus 2 SD, made no decisive difference. Hence, OCT positive cases were not adequately discriminated with MCA Doppler blood flow velocimetry, and BSF was not a good marker to identify candidates for cesarean delivery in cases with a negative OCT. When MCA blood flow is measured during rest, there is no difference in vascular flow resistance between OCT positive and OCT negative cases (9). BSF is a benign adaptive mechanism to cope with hypoxemia (6), so the poor agreement with the OCT result in the present study was no surprise.

In contrast to a majority of obstetricians, we continue to use the OCT and are content with the performance of the OCT (8). The clinical value of OCT in IUGR pregnancies was not evaluated in this study, but the 3% rate of low Apgar scores and cord blood acidosis associated with a 63% vaginal delivery rate in this group of high-risk pregnancies indicates it is a fair tool to select for mode of delivery. Updated figures on the value of OCT in IUGR pregnancies will be published in a forthcoming study.

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DISCLOSURE OF INTEREST

None stated.

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Table 1

Characteristics of 126 growth-restricted term fetuses with brain-sparing flow (BSF) and normal brain blood flow (non-BSF). For definition of BSF, see text. Figures are numbers, median (range) or mean ± SD. Statistics were performed with the chi-squared test, Fisher's exact test, or Mann-Whitney U test, as appropriate.

	BSF N = 27		Non-BSF N = 99		Significance of difference (p)
OCT positive	8	(29.8 %)	12	(12.1 %)	0.058
Median (range) days from last MCA Doppler to delivery[a]	0 (0-11)		1 (0-21)		0.1
Gestational age at delivery (days)	271 ± 9		275 ± 10		0.09
Vaginal delivery	10	(37.0 %)	66	(66.7 %)	0.01
Vaginal delivery in OCT negative	10/19	(52.6 %)	69/87	(79.3 %)	0.04
Apgar score 5 min <7	0	(0 %)	3	(3.0 %)	1.0
Arterial pH <7.10	0/19	(0 %)	2/71	(2.8 %)	1.0
Arterial pH <7.10 in vaginal delivery	0/10	(0 %)	1/66	(1.5 %)	1.0
Venous pH <7.15	0/21	(0 %)	3/90	(3.3 %)	1.0
Venous pH <7.15 in vaginal delivery	0/10	(0 %)	2/66	(3.0 %)	1.0
Birthweight (g)	2464 ± 285		2612 ± 340		0.03
NICU transfer	2	(7.4 %)	9	(9.1 %)	1.0

MCA = middle cerebral artery; NICU = neonatal intensive care unit; OCT = oxytocin challenge test

a) MCA Doppler and OCT performed on the same day

Table 2

Distribution of fetuses with brain-sparing flow (BSF) (N = 27) relative to the oxytocin challenge test (OCT) result and mode of delivery in 126 women with middle cerebral artery Doppler flow velocimetry recorded immediately before the OCT. Figures are number of cases.

	Ocytocin challenge test		Mode of delivery	
	Positive	Negative	Cesarean section	Vaginal delivery
All	20	106	47	79
Brain-sparing flow	8	19	17	10
Normal brain flow	12	87	30	69
OCT negative	-	106	27	79
Brain-sparing flow	-	19	9	10
Normal brain flow	-	87	18	69

Association between BSF and positive OCT: Positive predictive value = 8/27 = 29.6%; Sensitivity = 8/20 = 40%; Negative predictive value = 87/99 = 87.9%; Specificity = 87/106 = 82.1%; Cohen's kappa coefficient = 0.19 (95% confidence interval 0-0.44).

Association between BSF and cesarean section: Positive predictive value = 17/27 = 63%; Sensitivity = 17/47 = 36.2%; Negative predictive value = 69/99 = 69.7%; Specificity = 69/79 = 87.3%; Cohen's kappa coefficient = 0.26 (95% confidence interval 0.07-0.45).

Association between BSF and cesarean section in OCT negative women: Positive predictive value = 9/19 = 47.4%; Sensitivity = 9/27 = 33.3%; Negative predictive value 69/87 = 79.3%; Specificity 69/79 = 87.3%; Cohen's kappa coefficient = 0.23 (95% confidence interval

0-0.47).