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Middle versus anterior cerebral artery Doppler for the prediction of perinatal outcome and neonatal neurobehavior in term small-for-gestational-age fetuses with normal umbilical artery Doppler

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KEYWORDS: anterior cerebral artery; Doppler; intrauterine growth restriction; middle cerebral artery; perinatal outcome

ABSTRACT

Objective *To evaluate whether anterior cerebral artery (ACA) Doppler ultrasonography is superior to middle cerebral artery (MCA) Doppler in the prediction of perinatal outcome and neonatal neurobehavior in term small-for-gestational-age (SGA) fetuses with normal umbilical artery (UA) Doppler.*

Methods *MCA and ACA Doppler ultrasonography was performed in a cohort of SGA term fetuses with normal UA Doppler. Perinatal outcome and neonatal neurobehavioral performance were compared with a group of term appropriate-for-gestational age (AGA) infants. Neurobehavior was evaluated at 40 (± 1) weeks of corrected age with the Neonatal Behavioral Assessment Scale. Differences between the study groups were adjusted for potential confounding variables by multiple linear or logistic regression analyis.*

Results *A total of 199 newborns (98 SGA and 101 AGA) were included. Among the SGA fetuses, 28.6 and 17% had MCA and ACA redistribution, respectively. Cases with either type of redistribution had an increased risk for adverse outcome, with no differences in predictive performance between the two parameters. SGA fetuses with MCA redistribution compared with controls had an increased risk for abnormal neurobehavioral performance in motor (36 vs. 20%; adjusted* $P = 0.02$*) and state organization (25 vs. 17.5%; adjusted* $P = 0.03$*) areas. SGA fetuses with ACA redistribution had only an increased risk for abnormal neurobehavioral performance area in state organization compared with controls (30 vs. 17.5%; adjusted* $P = 0.021$*).*

Conclusion *In term SGA newborns with no signs of brain-sparing, ACA Doppler investigation does not provide any benefit over MCA in terms of the prediction of adverse perinatal outcome.* Copyright © 2010 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Small fetuses with normal umbilical artery (UA) Doppler ultrasound findings are currently defined as normal small-for-gestational-age (SGA) fetuses[1,2]. Earlier reports suggested that this diagnostic category might essentially contain constitutionally small fetuses[3], but recent evidence suggests that a substantial proportion of fetuses have true growth restriction[4]. Studies over the last decade have provided evidence that perinatal outcome may be significantly poorer in SGA fetuses[2–5,6]. Furthermore, there is an increased prevalence of abnormal neurobehavioral and neurodevelopmental tests in childhood, with similar features to those described for preterm children who had intrauterine growth restriction[4,7–9]. Since the identification of SGA fetuses with milder forms of growth restriction cannot be based on UA Doppler, the use of middle cerebral artery (MCA) ultrasonography might help to identify these cases[6,10,11]. Up to 20% of SGA fetuses have a reduced pulsatility index (PI) in the MCA, a sign that is associated with poorer perinatal outcome[6,11] and with an increased risk of abnormal neurobehavior at birth and at 2 years of age[7,12].

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Recent studies suggest that the anterior cerebral artery (ACA) could be a better predictor of adverse neurological outcome than the MCA[13]. The ACA supplies cortical and subcortical areas of the frontal lobe and has been found to be vasodilated in a proportion of SGA fetuses with normal MCA Doppler[14]. Studies assessing the temporal evolution of the brain arteries in intrauterine growth restricted (IUGR) fetuses suggest that the ACA shows vasodilatory changes earlier than does the MCA[14,15]. Furthermore, tissue perfusion studies in fetuses with IUGR suggest that increased frontal perfusion is the earliest response to brain hypoxia[16].

The aim of our study was to see whether ACA Doppler investigation is superior to MCA Doppler investigation in the prediction of adverse perinatal outcome in term SGA fetuses with normal UA Doppler.

METHODS

Subjects

A prospective cohort was created of all suspected SGA fetuses (estimated fetal weight below the 10th centile[17] at a routine third-trimester ultrasound scan) referred to our unit between January 2007 and October 2008. Inclusion criteria were: (1) singleton pregnancy; (2) absence of congenital malformations or chromosomopathies; and (3) normal UA-PI[18] at inclusion (PI $< 95^{th}$ centile for gestational age). Exclusion criteria were: (1) abnormal UA-PI[18] during the study period; and (2) birth weight above the 10^{th} centile according to local standards[19]. Appropriate-for-gestational age (AGA) controls were defined as singleton neonates with birth weight between the 10^{th} and 90^{th} percentiles according to local standards[19]. Controls were selected from our general population, with previous adequate ultrasound estimated fetal weight[17], individually matched with cases for gestational age at inclusion (± 1 week), corrected by first-trimester ultrasound[20]. Written consent was obtained in all cases and the study design was approved by the local ethics committee.

Management

For Doppler studies Siemens Sonoline Antares (Siemens Medical Systems, Malvern, PA, USA) or Voluson 730 Expert (GE Medical Systems, Milwaukee, WI, USA) ultrasound devices with 6–2- and 7–4-MHz curved array probes were used. In all cases ultrasound examination was performed by one of the three experienced observers (F.F., R.C.M. and D.O.). Pulsed Doppler parameters were generated automatically from three or more consecutive waveforms, with the angle of insonation as close to 0° as possible. A high-pass wall filter of 70 Hz was used to avoid artifacts. Umbilical Doppler investigations were performed at a free-floating cord loop, by means of image-directed pulsed and color Doppler. The circle of Willis was located by color Doppler imaging in the axial view of the fetal head at the level of the cerebral peduncles. MCA flow velocity waveforms were recorded at 1–2 cm from the circle of Willis, during the absence of fetal movements, at insonation angles of less than 30°. For the ACA, the Doppler gate was placed immediately after the origin of the ACA from the internal carotid artery. Either the MCA-PI or the ACA-PI values below the 5^{th} centile were considered indicative of cerebral blood flow redistribution and were reported as abnormal[18,21].

Only the last examination within 1 week of delivery was included in the analysis. Cases were managed at the discretion of an attending senior obstetrician, following standard management guidelines, who was blinded to the cerebral Doppler results. Induction of labor was performed by cervical ripening with prostaglandins for cases when either estimated fetal weight was below the 3^{rd} centile at term or an ultrasound estimated fetal weight below the 10^{th} centile was suspected at 40 weeks' gestation.

Neurobehavioral outcome

The Neonatal Behavioral Assessment Scale (NBAS) was used to prospectively assess all cases and controls at 40 ± 1 weeks of corrected age by one of three observers accredited by The Brazelton Institute (Harvard Medical School, Boston, USA). The observers were blinded to the study group and to Doppler status. The examination consisted of four behavioral areas rated on a scale of 1–9, where 9 is the best performance, except for some curvilinear scale items which, according to the manual, were rescored as linear on a 5, 6 or 8-point scale[22]. With the newborn between two feeds, in a small, quiet, semi-dark room at a temperature of between 22 and 27°C and in the presence of at least one parent, the following areas were analyzed: habituation (habituation to light, rattle, bell and tactile stimulation of the foot items); motor (which includes general tone, motor maturity, pull-to-sit, defensive movements and level of activity); social–interactive (which includes response to visual and acoustic stimuli); and state organization (which includes peak of excitement, rapidity of build-up, irritability and lability of states). The behavioral items were converted into percentiles according to normal curve references for our population[23], and each area was considered abnormal at a score below the 5^{th} percentile.

Statistical analysis

Student's *t*-test and Pearson's chi-squared test or Fisher's exact test were used to compare quantitative and qualitative data, respectively. Receiver–operating characteristics (ROC) curves were used to evaluate the diagnostic performance for adverse perinatal outcome of both arteries. Following standard methodology, neurobehavioral outcome was adjusted for smoking during pregnancy (no smoking; 1–9 cigarettes/day; 10+ cigarettes/day); labor induction; mode of delivery (Cesarean section vs. vaginal delivery); gestational age at birth; gender; and postnatal days at evaluation by multiple linear or logistic regression analysis. Statistical

analysis was performed using the SPSS 15.0 (SPSS Inc., Chicago, IL, USA) and MedCalc 8.0 (MedCalc Software, Broekstraat, Belgium) statistical software.

RESULTS

A total of 118 SGA fetuses fulfilled the inclusion criteria. Seven were excluded because of birth weight above the 10th centile; none had an adverse perinatal outcome. The remaining 111 cases were matched at delivery with 111 AGA babies. Of these, the parents of six cases and seven controls later declined to participate in the neurobehavioral evaluation. Finally, in seven cases and three controls the evaluation was not considered satisfactory by the examiner owing to the absence of a sleeping state during the test. Thus, a final total of 199 babies (98 SGA and 101 AGA) were tested.

Table 1 compares demographic characteristics by study group. Women in the SGA group had a lower body mass index and showed a non-significant trend to belong to a lower socioeconomic level.

Table 2 describes the clinical characteristics and perinatal outcome of the SGA group according to the MCA or ACA redistribution. A total of 28 (29%) and 17 (17%) SGA fetuses had MCA and ACA Doppler redistribution, respectively. It is of note that in 14 cases MCA and ACA simultaneously showed redistribution. Whereas ACA-redistributed fetuses had a lower birth weight than non ACA-redistributed fetuses, no differences were observed between MCA-redistributed and non MCA-redistributed fetuses. Both MCA and ACA redistribution accounted for significant differences in the incidence of Cesarean section, and only the MCA significantly differentiated cases at risk for fetal distress. Figure 1 shows the ROC curves of MCA and ACA for the prediction of adverse outcome. Both parameters showed significant areas under the curve (0.71 (95% CI, 0.6–0.81) for ACA-PI and 0.72 (95% CI, 0.61–0.82) for MCA-PI), and pairwise comparison of both areas showed no significant differences between the two parameters ($P = 0.82$).

Neurobehavior was assessed at 6.2 (± 4.9) and 14.4 (± 9.04) days of age in the AGA and SGA groups, respectively. Table 3 shows the NBAS score by area and study group, where motor, social and state organization differed significantly between the AGA and SGA groups. These differences remained significant after adjustment for potential confounders for motor and state organization. Figure 2 summarizes the NBAS scores for AGA and SGA fetuses with and without redistribution according to MCA and ACA Doppler. Among SGA fetuses, cases with MCA redistribution showed significantly lower NBAS in motor (adjusted $P = 0.03$) and state organization (adjusted $P = 0.025$) areas than the SGA fetuses without redistribution. On the other hand, a non-significant trend towards lower scores was observed in ACA-redistributed fetuses only in the state organization area.

Figure 3 shows the frequency of abnormal NBAS. Among SGA fetuses, cases with MCA redistribution showed an increased risk for abnormal motor (36 vs. 20%; adjusted $P = 0.023$) (adjusted OR, 3.94 (95% CI, 1.21–12.8)) and state organization (25 vs. 17.5%; adjusted $P = 0.025$) (adjusted OR, 4 (95% CI, 1.19–13.3)) areas than the SGA without redistribution.

Table 1 Population demographic characteristics

Characteristic	*Control group (n = 101)*	*SGA group (n = 98)*	P*
MA at delivery (years)	31.8 ± 4.9	31.2 ± 5.1	0.44
Primiparous	61.0	67.3	0.35
Caucasian	78.2	78.6	0.95
Male: female ratio of fetuses	49.5 : 50.5	54.1 : 45.9	0.52
BMI at booking (kg/m^2)	23.4 ± 3.7	21.99 ± 3.5	0.01
Height (cm)	162.6 ± 6.3	160.5 ± 7.3	0.06
Low socioeconomic level†	9.3	18.5	0.06
Smoker	15	19.4	0.42
GA at birth (days)	279 ± 7.9	265 ± 9.5	< 0.001
Birth weight (g)	3339 ± 390.7	2382 ± 263.7	< 0.001
Pre-eclampsia	0	8.2	0.003
Cesarean section	25	37.1	0.06
Induction of labor	18	71.1	< 0.001
Composite adverse outcome‡	19.8	34.7	0.02

Values given as mean ± SD or %. *Student's *t*-test for independent samples, Pearson's χ^2 test or Fisher's exact test, as appropriate. †Routine occupations, long-term unemployment or never worked (UK National Statistics Socio-Economic Classification[34]). ‡Composite adverse outcome based on the presence of at least one of the following: intervention for fetal distress, umbilical artery pH < 7.10, need for neonatal resuscitation or admission to neonatal intensive care unit. BMI, body mass index; GA, gestational age; MA, maternal age.

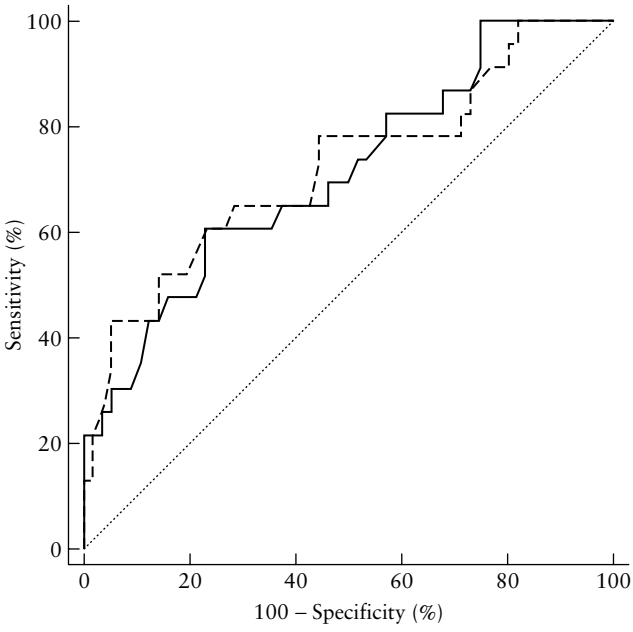

Figure 1 Receiver–operating characteristics curves of middle (– – –) and anterior (———) cerebral arteries for the prediction of adverse outcome.

Table 2 Clinical characteristics and perinatal outcome of small-for-gestational-age neonates according to middle (MCA) or anterior (ACA) cerebral artery redistribution

	MCA			*ACA*		
Characteristic	*Not redistributed (n = 70)*	*Redistributed (n = 28)*	P*	*Not redistributed (n = 81)*	*Redistributed (n = 17)*	P†
GA at birth (days)	266 ± 9.9	265 ± 8.7	1	266 ± 9.5	262 ± 8.7	0.1
Birth weight (g)	2411 ± 246.6	2310 ± 294.4	0.54	2426 ± 235.2	2173 ± 296.5	0.01
Birth weight < 3rd centile	31 (44.3)	18 (64.3)	0.07	39 (48.1)	10 (58.8)	0.42
Head circumference (cm)	32.7 ± 1	32.3 ± 1	0.41	32.6 ± 1	32.3 ± 1	0.99
Pre-eclampsia	5 (7.1)	3 (10.7)	0.68	5 (6.2)	3 (17.6)	0.14
Induction of labor	52 (74.3)	17 (60.7)	0.14	58 (71.6)	10 (58.8)	0.25
Cesarean section	18 (25.7)	18 (64.3)	0.001	24 (29.6)	12 (70.6)	0.002
Intervention for fetal distress	10 (14.3)	12 (42.9)	0.006	15 (18.5)	7 (41.2)	0.06
5-min Apgar score < 7	0	0	1	0	0	1
Umbilical artery pH < 7.10	4 (5.7)	2 (7.1)	0.65	4 (4.9)	2 (11.8)	0.26
Neonatal resuscitation	2 (2.9)	4 (14.3)	0.09	3 (3.7)	3 (17.6)	0.07
NICU admission	1 (1.4)	2 (7.1)	0.2	1 (1.2)	2 (11.8)	0.08
Composite adverse outcome‡	14 (20.0)	13 (46.4)	0.01	20 (24.7)	8 (47.1)	0.05

Values given as mean ± SD or %. *P* determined by Student's *t*-test for independent samples, Pearson's χ^2 or Fisher's exact test, as appropriate: *between MCA groups; †between ACA groups. ‡Composite adverse outcome based on the presence of at least one of the following: intervention for fetal distress, umbilical artery pH < 7.10, need for neonatal resuscitation or admission to NICU. GA, gestational age; NICU, neonatal intensive care unit.

Finally, the frequency of abnormal NBAS significantly differed between cases with and without ACA redistribution only for the organization of the state area (30 vs. 17.5%; adjusted $P = 0.021$) (adjusted OR, 5 (95% CI, 1.28–20)).

Table 3 Neurobehavioral scores by area and study group

Parameter	*Control group (n = 101)*	*SGA group (n = 98)*	P*	P†
Habituation	6.85 ± 1.6	6.49 ± 1.67	0.18	0.93
Social	6.72 ± 1.4	5.59 ± 1.41	< 0.001	0.16
Motor	5.73 ± 0.75	5.29 ± 0.84	< 0.001	0.04
State organization	4.39 ± 1.08	3.86 ± 1.28	0.002	0.012

Values given as mean ± SD. *Student's *t*-test. †Adjusted for smoking during pregnancy, mode of delivery, gestational age at birth, gender and postnatal days at evaluation by linear regression. SGA, small-for-gestational age.

DISCUSSION

This is the first study to explore the capacity of the ACA to predict perinatal and neurobehavioral outcome in term SGA fetuses. Contrary to the hypothesis of the study, we found no differences between MCA and ACA redistribution in terms of association with perinatal outcome or neonatal neurobehavioral performance. Therefore, MCA seems to remain unchallenged as a primary clinical tool for evaluating term SGA fetuses without signs of placental insufficiency.

We have previously demonstrated that in preterm IUGR fetuses ACA vasodilation takes place earlier than MCA vasodilation[15]. Dubiel *et al.*[14] reported similar results in pregnancies with pregnancy-induced hypertension. These findings are not in line with the results of the present study. However, different population characteristics are likely to explain this inconsistency. The above studies included a substantial proportion of early-onset growth restricted fetuses with abnormal UA Doppler. Since gestational age was considerably different we cannot exclude differences in the temporal patterns in the adaptation to chronic hypoxia due to maturity changes in brain hemodynamic regulation. Indeed, Dubiel *et al.*[14] reported a better correlation of ACA-PI with adverse perinatal outcome only for cases before 32 weeks' gestation. For those delivering beyond that gestational age MCA-PI and ACA-PI showed a similar association with perinatal outcome. Also in line with this reasoning, other studies have found no differences between ACA and MCA in response to acute hypoxia in term SGA fetuses[24]. As a secondary explanation, the considerable degree of systemic fetal hemodynamic adaptation to hypoxia in early-onset IUGR, which is not present in term SGA, could also influence brain hemodynamics in ways that we cannot interpret.

This study confirms previous reports suggesting that late-onset SGA is associated with an increased risk of abnormal neonatal neurobehavior and neurodevelopment in childhood[7,13,25–27]. Furthermore, we have previously described that in late-onset SGA fetuses, MCA redistribution differentiates those at risk of long-term suboptimal neurodevelopment[7]. In a recent study, Roza *et al.*[13] showed that fetal ACA redistribution could be superior to MCA in the prediction of neurobehavioral problems in childhood. In the present study MCA and ACA Doppler were similarly associated with poorer neonatal neurobehavior. These findings are difficult to compare with those of Roza *et al.* for two reasons. Our results refer exclusively to neonatal neurobehavior and therefore

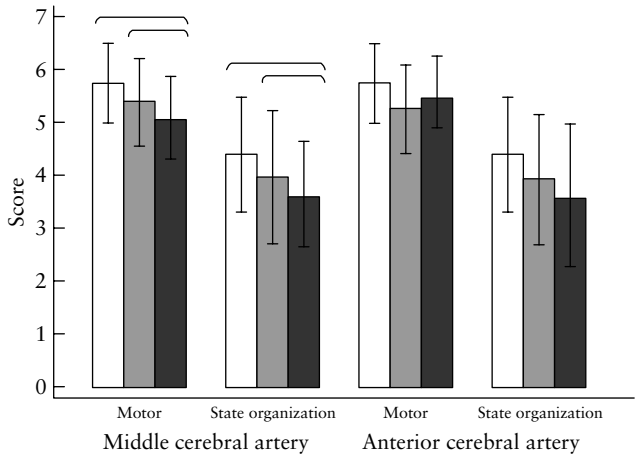

Figure 2 Neurobehavioral scores (mean and SD) according to area and study group: appropriate-for-gestational-age fetuses (□), small-for-gestational-age (SGA) fetuses without redistribution (▒) and SGA fetuses with redistribution (■). Long brackets indicate significant adjusted linear trend; short brackets indicate significant adjusted difference between SGA groups.

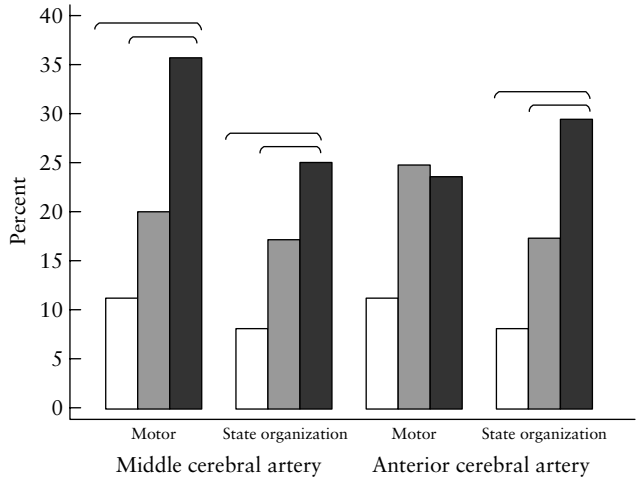

Figure 3 Frequency of abnormal neurobehavioral performance according to area and study group: appropriate-for-gestational-age fetuses (□), small-for-gestational-age (SGA) fetuses without redistribution (▒) and SGA fetuses with redistribution (■). Long brackets indicate significant adjusted linear trend; short brackets indicate significant adjusted difference between SGA groups.

they do not exclude the possibility that long-term assessment could demonstrate a higher sensitivity of ACA in predicting poor neurodevelopment. A second important difference is that the study of Roza *et al.*[13] was based on a large cohort that included all pregnancies, not only SGA fetuses. Therefore, the value of ACA for the prediction of long-term outcome in small fetuses remains to be evaluated.

The findings of this study may appear inconsistent with evidence pointing to a higher vulnerability of frontal areas in fetuses with IUGR[9,28–31]. However, the arteries we evaluated provide the blood supply to ill-defined anatomical areas with a marked component of vascular shunting. Tissue perfusion depends on local arteriolar phenomena and therefore the data cannot be used to infer which territories are specifically affected by vascular changes. Using the fractional moving blood volume estimate to assess tissue perfusion we have previously suggested that increased perfusion in the frontal lobe seems to be the earliest response to hypoxia, rather than changes in basal ganglia perfusion[16]. It is not known whether evaluation of tissue perfusion can detect subtle differences in blood perfusion between cerebral areas in this population of late-onset SGA. Studies evaluating the potential role of direct measurements of perfusion towards different brain regions in this population are under way.

This study has some limitations. First, since Doppler ultrasonography was not performed in the AGA babies, we cannot rule out the possibility that some fetuses in this group might have shown brain redistribution. However, this potential bias would be conservative, attenuating the differences between AGA and SGA fetuses. Secondly, although NBAS is a gold standard for the evaluation of the neonate's capacity to respond to the environment, reflecting brain maturation, it only assesses neurobehavioral and not cognitive function. However, several studies have demonstrated the correlation between neonatal neurobehavioral performance and later neurocognitive development[8,9,27,32,33]. We admit that socioeconomic status may have confounded the association between SGA and abnormal neurobehavior. However, although socioeconomic status is a major determinant of postnatal neurobehavior during childhood its influence in the neonatal period is still minimal if smoking is accounted for in our population[23]. Thirdly, any clinical study on the surveillance of fetal growth needs to be interpreted with caution because it can never be entirely blinded, and the clinical management is influenced by the antenatal findings. This work-up bias could account for differences between AGA and SGA. However, the clinicians attending the deliveries were unaware of the MCA or ACA Doppler status. Thus this potential bias could not explain differences between the two groups of SGA fetuses. Besides, the neurobehavioral assessment could also have been biased by the examiners' knowledge of perinatal factors. However, since these examiners were also blinded to the antenatal Doppler findings and because birth weight was similar between the two groups, this expectation bias is unlikely to explain differences between the Doppler groups.

In conclusion, the findings of this study do not support the inclusion of ACA Doppler investigation in the management of term SGA fetuses.

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