Use of conditional centiles of middle cerebral artery pulsatility index and cerebroplacental ratio in the prediction of adverse perinatal outcomes

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Key words

Conditional centile, middle cerebral artery, cerebroplacental ratio, pulsatility index, perinatal outcomes

Abbreviations

aRR, adjusted relative risk; CI, Confidence interval; CPR, cerebroplacental ratio; MCA, middle cerebral artery; NICU, neonatal intensive care unit; PI, pulsatility index; RR, relative risk; SGA, small for gestational age; UA, umbilical artery.

Key message

The centiles ≤10 of the cerebroplacental ratio and corresponding conditional centiles (conditioned by the previous measurement) have independent effects, and their combination improves the prediction of adverse perinatal outcomes, probably because now the individual change over time has been included.

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Conflict of interest

The authors did not report any conflict of interest.

Abstract

Introduction: Centiles of middle cerebral artery (MCA) pulsatility index (PI) and cerebroplacental ratio (CPR) are useful for predicting adverse perinatal outcomes. A 'conditional centile' is conditioned by a previous measurement reflecting degree of individual change over time. Here we test whether such centiles are independent predictors and whether their combination improves prediction.

Material and Methods: This prospective longitudinal study included 220 pregnant women diagnosed with or at risk of having an SGA fetus. Serial Doppler measurements of the umbilical artery (UA) and MCA PIs were used to calculate CPR. Preterm birth, operative delivery due to fetal distress, admission to neonatal intensive care unit, 5-min Apgar score <7, newborn hypoglycemia and perinatal mortality were considered adverse outcomes. Possible associations were analyzed by log-binomial regression analysis.

Results: Serial Doppler measurements of the MCA were available in 207 participants and CPR in 205. Conditional centile ≤5 and ≤10 for both MCA PI and CPR were associated with increased risk for adverse perinatal outcomes. However, only the combination of CPR centile and conditional centile ≤10 showed a better performance in the prediction of operative delivery due to fetal distress ($p = 0.032$), admission to NICU ($p = 0.048$), and the combined variable "any adverse outcomes" ($p = 0.034$) compared with the use of centile ≤10 alone.

Conclusions: Conditional centile for MCA PI and CPR ≤5 and ≤10 are associated with adverse perinatal outcomes. When adding conditional centile to conventional centile for CPR, the prediction improved compared with the use of conventional centile alone.

Introduction

Doppler ultrasonography of the umbilical artery (UA) and middle cerebral artery (MCA) are integrated in the surveillance of high risk pregnancies. A high UA pulsatility index (PI) is associated with perinatal morbidity (1). Low PI in the MCA reflects vasodilation in the brain, and signifies fetal redistribution of the cardiac output to the brain, the effect is termed brain sparing and the finding is associated with increased risk of adverse perinatal outcomes (2, 3). Although high UA PI and low MCA PI each are associated with increased risk of adverse perinatal outcomes (1, 4, 5), recent studies have shown that combining these two parameters in the cerebroplacental ratio (CPR) further improves the prediction (4, 6-10). The predictive value of CPR has been shown to be of value not only in the surveillance of SGA fetuses, but also in fetuses that are appropriate for gestational age (AGA) (11). However, the results of using CPR $<5^{th}$ centile to predict adverse perinatal outcome varies between different studies, the sensitivity varying between 42 and 85% (12-14). We have recently shown that adding conditional centiles to the conventional centiles for fetal size improves the prediction of adverse outcomes in pregnancies with an SGA fetus or at risk thereof (15). Since the conditional centile is calculated based on a previous measurement, it introduces the information of growth development. In the same way, the use of conditional centiles in the evaluation of Doppler measurements may add the information on temporal development that may influence risk of adverse perinatal outcome. If so, the clinician would more fully exploit the information that lies in the longitudinal nature of the measurements used for monitoring.

Thus the aim of the present study was to test the hypothesis that the conditional centiles for MCA PI and CPR were independently associated with adverse perinatal outcomes, and that combining conventional and conditional centiles improves the prediction of adverse perinatal outcomes compared with the use of conventional centiles alone in a high-risk population.

Material and methods

The present study is part of a larger prospective longitudinal project “Fetal Growth and Perinatal Outcome” that included pregnant women at increased risk of having an SGA fetus, or who already had been diagnosed with SGA. We have recently published the data from the same study on growth and size (15), while here we examine the association between serial Doppler measurements and perinatal outcome. The study was carried out between May 2010 and June 2014 at the Fetal Medicine Unit, Haukeland University hospital, Bergen, Norway. The study protocol was approved by the Regional Committee for Medical and Health

Research Ethics (approval no. REC West 2010/686), and written informed consent was obtained from all the women who participated. Women with a singleton pregnancy who were referred for a 24-weeks ultrasound scan due to increased risk of having an SGA, and women who were diagnosed with an SGA fetus ($\leq 5^{th}$ centile) (16) were invited to join the study. A history of pre-eclampsia, giving birth to a SGA neonate (birth weight of $\leq 5^{th}$ centile) (16), chronic maternal disease such as hypertension, renal failure, systemic and rheumatic disorder or a discrepancy of ≥14 days between the gestational age set by LMP and that calculated via ultrasound, were factors considered to increase the risk of having an SGA fetus in the present pregnancy. Cases with congenital malformation and chromosomal aberration were excluded.

Gestational age was based on a second trimester head circumference ultrasound measurement (17) unless a first-trimester scan of crown rump length (18) had determined fetal age, or day of conception was known due to conception by in vitro fertilization. Voluson 730 Expert, E6 and E8 (GE Medical Systems, Kretz Ultrasound, Zipf Austria) systems were used for the ultrasound measurements. The PI of the UA and MCA were measured at each visit and the corresponding centiles calculated (19, 20). The intervals of repeated examinations were individualized according to clinical needs, but we aimed to schedule examinations at least every sixth week. In the analysis we included only those who had ≥2 measurement since at least two observations are necessary to calculate a conditional centile. CPR was calculated as MCA PI divided by UA PI (21) and their corresponding centiles calculated according to Ebbing et al (20). Preterm birth (<37 weeks of gestation), operative delivery due to fetal distress, admission to the neonatal intensive care unit (NICU), 5-min Apgar score <7, hypoglycemia (glucose <2.0 mmol/L), and perinatal mortality were considered adverse outcomes for the newborn. A combined outcome variable of "any adverse outcomes" was established for each pregnancy provided at least one component was abnormal. Perinatal data was collected from clinical records after birth. Delivery due to fetal distress included cesarean and vaginal instrumental delivery and was indicated by pathological fetal Doppler findings, cardiotocography (CTG) abnormalities or due to fetal echocardiographic events (S-T analysis, STAN® (22)) during labor. Fetal surveillance using S-T analysis was restricted to risk pregnancies ≥36 weeks of gestation, otherwise surveillance during labor was performed by intermittent or continuous CTG recording. Newborns with gestational age <34 weeks were routinely transferred to the NICU.

Conditional centiles (23) for MCA PI and CPR can be calculated from any previous measurement. The formula for a conditional centile includes gestational age, measurement and variance at the previous and current sessions in addition to the covariance of both measurements. In this study we chose to condition the last measurement based on the penultimate measurement (Figure 1). Log-binomial regression analysis was used to test the association between conditional centiles ≤5 or ≤10 for MCA PI and CPR at the final visit and adverse outcomes; the results are presented as relative risk (RR) with 95% confidence intervals (CI). To test whether the centiles at the final visit and the corresponding conditional centiles ≤5 and ≤10 had independent association with the adverse outcomes, both the conventional and the conditional centiles were included in the model, and thereby adjusted for each other; the results are presented as adjusted Relative Risk (aRR). In cases where both centiles had independent association with the outcomes, we were able to test the hypothesis that adding conditional centile to conventional centile for MCA PI and CPR improved the prediction of adverse outcomes compared with the use of conventional centile alone. Goodness of fit of the two models was compared using Log-likelihood testing.

To increase the sample size when log-binomial regression failed to show independent associations, all observations were used in multilevel log-binomial regression. Pairs of first to second, second to third, third to fourth, fourth to fifth, and fifth to sixth measurements were identified. We calculated conventional centiles and conditional centiles (5^{th} and 10^{th}) for the last measurement of CPR and MCA PI in each pair. Log-likelihood is not optimal in multilevel models. The possible improvement of the model adding conditional centiles to conventional centiles was instead assessed by change in Wald chi square between the models. To optimize these calculations we used Markov Chain Monte Carlo regression in the MLwiN program.

Positive and negative predictive value in addition to sensitivity and specificity were used to test the diagnostic usefulness. Possible collinearity between conventional and conditional centiles was assessed using variance inflation factor (24). Statistical analyses was performed using SPSS 22 (Statistical Package for the Social Sciences, SPSS, Chicago, IL, USA), and the MLWin program (MLWin, Centre for Multilevel Modelling, University of Bristol, Bristol, UK). The threshold for significance was set to $p < 0.05$.

Results

Seven of the 227 women who were invited to the study declined to participate. Three participants were excluded due to congenital malformations identified after birth. One woman withdrew when she moved out of the hospitals catchment area. Serial measurements of MCA PI was missing for nine women, for the CPR this number was 11, which provided us with data from 207 and 205 participants eligible for analysis. Of the 207 participants 156 were included due to high risk of having an SGA newborn, of these 69 had a history with pre-eclampsia; 131 had given birth to an SGA newborn (birth weight ≤5th centile); nine were included due to chronic maternal disease and two were included because of a discrepancy of ≥14 days between LMP and ultrasound dating. Fifty-three participants fulfilled more than one inclusion criteria. Fifty-one were included due to prenatal identification of a fetus ≤5th centile.

Nineteen doctors with basic to advanced training in Doppler examination performed the measurements. A total of 865 observation of MCA PI was available and 851 observations of the CPR. The number of neonates with a birthweight ≤5th centile (25) was 83; two of these had only one CPR observation and were not included in the analysis. The number of observations in these 83 SGA newborns was 311 for MCA PI and 304 for CPR. Of the SGA newborns 29% had an UA PI ≥95th centile, 31% had an MCA PI ≤5th centile and 47% had CPR centile ≤ 5 at the last visit. In those with normal birthweight the frequency of pathologic Doppler was 4%, 6% and 7%, respectively. Detailed information on maternal characteristics and birth outcomes have been published previously (15) and for the 207 participants with serial Doppler measurements characteristics are presented in Table 1. Outcome data was complete for all variables, except for 39 (18.8%) missing neonatal glucose levels. Of the 207 participants a total of 87 (42.0%) had at least one adverse outcome, 49 (23.7%) had a preterm birth, 50 (24.2%) had an operative delivery due to fetal distress, 47 (22.7%) were admitted to NICU. 12.5% (21 out of 168) had neonatal hypoglycemia and 10 (4.8%) had a 5-min Apgar score <7. Two (1.0%) newborns died in the neonatal period, both were severely growth restricted and were born before 28 weeks gestation.

Collinearity between conventional and conditional centiles was within acceptable level (variance inflation factor <10) for both MCA PI and CPR for the 5th and 10th centile. Our results showed an association between a low centile for MCA PI and adverse perinatal outcomes (Table 1). In addition we found that conditional centiles ≤5 and ≤10 for MCA PI were associated with increased risk of preterm birth, operative delivery due to fetal distress, admission to NICU, 5 minute Apgar score <7 and the combined outcome variable 'any adverse outcome' (Table 2). The study was too small to study the associated risk of hypoglycemia and perinatal deaths. When both conventional and conditional centiles were included in the model, conditional centiles for MCA PI ≤5 and ≤10 had no independent association with the outcomes. However, when including conditional centile ≤5 for MCA PI from the entire series of measurements in multilevel log-binomial regression analysis (639 pairs of observations) we demonstrated an independent effect and a doubled risk of operative delivery due to fetal distress, aRR 2.0 (95% CI; 1.1-3.4), but adding conditional centile ≤5 did not improve the prediction.

Similar to the analysis of MCA PI, the conventional and conditional centiles ≤5 and ≤10 for CPR were both associated with adverse perinatal outcomes, except for low 5-min Apgar score (Table 3). When both parameters were included in the model, the conventional and conditional centiles ≤10 had independent effects on risk of adverse perinatal outcomes (Table 4), while conditional centile ≤5 for CPR had no independent effect on the outcomes. Combining conventional centile and conditional centile of CPR ≤10 resulted in a significant improvement (log-likelihood test) in the prediction of operative delivery due to fetal distress, admission to the NICU, and 'any adverse outcomes'. For preterm birth only the conditional centile ≤10 for CPR had independent effect when the conventional and conditional centiles were included in the model (Table 4).

Positive predictive value for CPR conventional centile ≤10 in predicting 'any adverse outcome' was 73.3% (95% CI; 61.0-82.9) and 81.3% (95% CI; 68.1-89.8) when conditional centile ≤10 was added. The sensitivity for conventional centile of CPR ≤10 as predictor of 'any adverse outcome' was 51.8% (95% CI; 41.3-62.1). Adding conditional centile of CPR ≤10 did not change sensitivity significantly: 45.9% (95% CI; 35.7-56.4) nor the specificity, which was 86.7% (95% CI; 79.4-91.6) and 92.5% (95% CI; 86.4-96.0), respectively.

Discussion

The present study shows that conditional centile ≤10 for CPR, which brings in the individual temporal dynamics into the prediction, had an independent effect on several perinatal outcomes and prediction was improved when combining the conditional and conventional centiles compared with the use of a conventional centiles alone. Conditional centile of MCA PI ≤5 had independent effect on risk of operative delivery due to fetal distress only when all observations were included in multilevel analysis.

It is of interest to note that while conditional and conventional centiles for fetal size had independent effects on the prediction of adverse neonatal outcome (15), this was not always the case for conditional and conventional centiles for MCA PI and CPR. The explanation may be found in the variance. In contrast to variation in fetal size, the individual physiological variation of the MCA PI and CPR in a normal pregnancy covers most of the variation span for the entire low-risk population (Figure 1), which implies high numbers of observations are needed to power the statistics. We had a sizeable study population powered for the fetal size and growth analysis, but it is likely that an even higher power would be needed for the MCA.

The wide range in sensitivity applying CPR in prediction of adverse outcomes (12-14) may be due to the wide physiological range of individual variation particularly for MCA PI (20). In delivery decisions CPR plays an important role, thus the decision varies between centers and between specialists (26). In agreement with other studies (4, 6, 7) we found that CPR appears to be a better predictor of adverse perinatal outcomes than MCA PI. The association between low centiles for MCA PI and CPR and adverse outcomes are well known (4, 6-8, 14), but this study adds new information on the value of exploiting the temporal dynamics that lies in serial observations, which is the basis for conditional centiles.

Low CPR has been shown to be associated with low umbilical cord pH in SGA newborns as well as in AGA (27). However, other studies did not support CPR as a screening tool in the third trimester of low-risk pregnancies (28, 29). In our study a considerable proportion of the neonates were AGA at birth, however, since our participants were a high-risk population, our results can only be considered valid for similar high-risk populations. Doppler measurements were performed by 19 doctors; which increased the variation but also the external validity of the study.

In line with local and national guidelines the finding of "brain sparing", i.e. MCA PI or CPR $\leq 5^{th}$ centile, prompted closer surveillance or delivery in late preterm and term pregnancies in our department, and managing clinicians were not blinded for the Doppler findings. This may have biased the relationship with the adverse outcomes, while the conditional centile for MCA PI and CPR were not available for clinicians, and therefore a less likely source of bias.

Our results support that low conditional centile for CPR is an independent predictor of adverse perinatal outcomes in addition to low conventional centile for CPR. However, further evidence of the usefulness of conditional centiles is needed to justify a recommendation for clinical practice. Should we suggest its practical application, it would be in cases with an indication for Doppler examination (e.g. fetal growth-restriction). In such a case a CPR $<5^{th}$ centile is associated with increased perinatal risks. The addition of a conditional centile would reflect the development. Thus a normal conditional centile would be reassuring while ≤ 5 would indicate a deteriorating development. The system may be used in normally growing fetuses, but we expect the usefulness rather will be found in the high-risk group.

We have shown an association between low conditional centiles for MCA PI and CPR and several adverse perinatal outcomes in a high risk population. The conditional centile of CPR is an independent predictor of outcomes that reflects temporal dynamics, but the large individual variation in fetal cerebral blood flow limits the test performance. However, our results indicate that there is merit in a further development of using serial observations to improve the prediction of adverse perinatal outcome.

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Table 1. Maternal characteristics and birth outcomes of the total study population (n = 207).

Characteristic	Median (range) or n (%)
Maternal	
Age (years)	30 (17–43)
Height (cm)	165 (148–179)
Pre-pregnancy weight (kg)	63 (44–120)
BMI (kg/m^2)	23 (17–42)
Smoking	17 (8%)
Newborn	
Gestational age at delivery (weeks^{+days})	39^{+2} (25^{+3}–42^{+3})
Newborn birth weight (g)	2890 (440–4340)
Newborn length (cm)	48 (28–54)
Male infants	101 (49%)

Table 2. Log binomial regression of conventional and conditional MCA PI centiles ≤5 and ≤10 and association with adverse outcomes in the total study (n = 207).

	Centile ≤5 (n = 33)				Conditional centile ≤5 (n = 20)				Centile ≤10 (n = 46)				Conditional centile ≤10 (n = 41)			
Outcomes	*n*	%	RR	95% CI	*n*	%	RR	95% CI	*n*	%	RR	95% CI	*n*	%	RR	95% CI
Preterm birth	25	76	5.5	6.6-8.3	16	80	4.5	3.1-6.6	29	63	5.1	3.2-8.1	27	66	5.0	3.2-7.8
OD due to fetal distress	21	64	3.8	2.5-5.8	14	70	3.6	2.4-5.5	27	59	4.1	2.6-6.4	24	59	3.7	2.4-5.8
NICU	24	73	5.5	3.6-8.5	15	75	4.4	2.9-6.6	28	61	5.2	3.2-8.3	27	66	5.5	3.4-8.7
5 min Apgar <7	5	15	5.3	1.6-17.2	3	15	4.0	1.1-14.3	7	15	8.2	2.2-30.3	6	15	6.1	1.8-20.5
Any adverse outcome	27	82	2.4	1.8-3.1	18	90	2.4	1.9-3.1*	34	74	2.2	1.7-3.0	32	78	2.4	1.8-3.1

* RR is calculated by cross table when regression analysis failed due to unsatisfied converge criteria.

OD, Operative delivery

Table 3. Log binomial regression analysis of conventional and conditional CPR centiles ≤5 and ≤10 and association with adverse outcomes in the total study population (*n* = 205).

	Centile ≤5 (*n* = 47)				Conditional centile ≤5 (*n* = 38)				Centile ≤10 (*n* = 60)				Conditional centile ≤10 (*n* = 51)			
Outcomes	*n*	%	RR	95% CI	*n*	%	RR	95% CI	*n*	%	RR	95% CI	*n*	%	RR	95% CI
Preterm birth	32	68	7.2	4.3-12.1	29	76	7.1	4.4-11.3	33	55	5.7	3.3-9.9	33	65	7.1	4.2-12.2
OD due to fetal distress	29	62	5.1	3.2-8.3	24	63	4.4	2.8-6.8	31	52	4.4	2.6-7.3	29	57	4.6	2.8-7.5
NICU	32	68	8.3	4.7-14.4	30	79	8.8	5.3-14.6	33	55	6.6	3.7-12.0	31	61	6.7	3.9-11.5
Any adverse outcome	39	83	2.9	2.2-3.8	34	90	2.9*	2.3-3.8	44	73	2.6	1.9-3.5	40	78	2.7	2.0-3.6

* RR is calculated by cross table when regression analysis failed due to unsatisfied converge criteria.

OD, Operative delivery

Table 4. Log binomial regression analysis of conventional and conditional centile ≤10 of CPR and their combination in the prediction of preterm birth, operative delivery due to fetal distress, admission to NICU and any adverse outcomes.

Outcome	CPR		Total *n*	Outcome *n*	Outcome %	Adjusted* relative risk	95% CI
Preterm birth							
	Centile	≤10	60	33	55	1.5	0.7-3.3
		>10	145	14	10	1	Reference
	Conditional centile	≤10	51	33	65	5.1	2.2-11.8
		>10	154	14	9	1	Reference
Operative delivery due to fetal distress							
	Centile	≤10	60	31	52	2.1	1.1-4.3
		>10	145	17	12	1	Reference
	Conditional centile	≤10	51	29	57	2.5†	1.3-4.8
		>10	154	19	12	1	Reference
Admission to NICU							
	Centile	≤10	60	33	55	2.8	1.3-6.3
		>10	145	12	8	1	Reference
	Conditional centile	≤10	51	31	61	2.9†	1.4-6.1
		>10	154	14	9	1	Reference
'Any adverse outcome'							
	Centile	≤10	60	44	73	1.7	1.0-2.8
		>10	145	41	28	1	Reference
	Conditional centile	≤10	51	40	78	1.8†	1.1-2.9
		>10	154	45	29	1	Reference

*The two independent parameters, centile at the final visit and conditional centile, are both included in the analysis.

†Inclusion of conditional centiles in the model in addition to final centiles significantly improved the prediction of operative delivery due to fetal distress ($p = 0.032$), admission to NICU ($p = 0.048$) and any adverse outcome ($p = 0.034$), log-likelihood test

CI, confidence interval

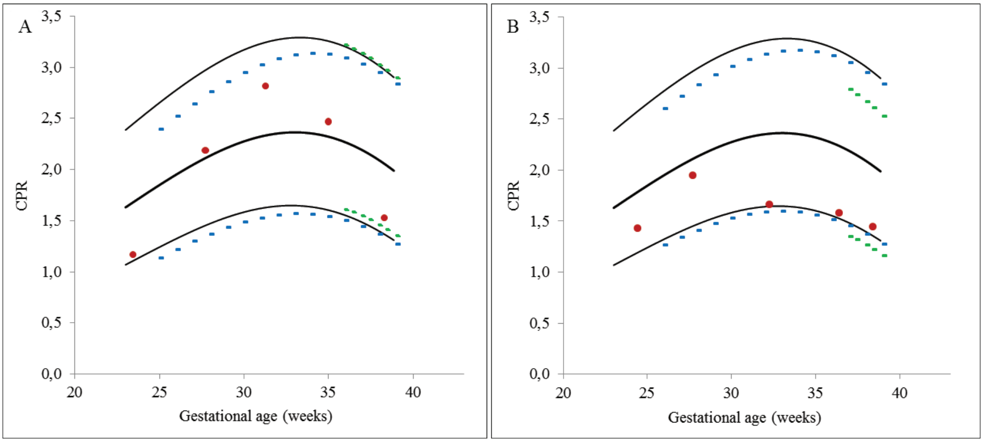

Figure 1. Individual serial measurements of cerebroplacental ratio (CPR) (red circles) for two of the participants in the study population (A: birthweight 4020 g, 90^{th} centile, and B: 3070 g, 10^{th} centile) plotted on the background of the 95^{th}, 50^{th} and 5^{th} reference centiles (black lines) (20). The individual 95^{th} and 5^{th} conditional centiles are calculated based on the first measurement (blue broken lines) or on the penultimate measurement (green broken lines). Note that the conditional ranges are marginally narrower than those for the background population, signifying that the individual variation normally is almost as large as that of the entire population.