Published online: 2018-07-06

Normogram of Middle Cerebral Artery Doppler Indexes and Cerebroplacental Ratio at 12 to 14 Weeks in an Unselected Pregnancy Population

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Am J Perinatol 2019;36:155–160.

Abstract

Objective The aim of this study is to assess the feasibility of visualizing the middle cerebral artery (MCA), establishing the normogram for MCA pulsatility index (PI) and peak systolic velocity (PSV), and calculating cerebroplacental ratio (CPR) at 12 to 14 weeks.

Study Design Prospective cross-sectional study on 186 gravidas presenting for nuchal translucency (NT) assessment. Maternal body mass index (BMI), fetal crown-rump length (CRL), biparietal diameter (BPD), and NT were obtained. Color Doppler was utilized to visualize the MCA and measure PI, PSV, and umbilical artery PI. Normograms for MCA PI and PSV, and for CPR, were constructed. Regression analysis was used for the reference range of MCA PI and CPR according to CRL and BPD. Chi-square and *t*-test were utilized. *p*-Value of < 0.05 was considered significant.

Results MCA was successfully visualized in 176/186 (94.6%), PI and PSV measured on 148/186 (79.6%) and 145/186 (78.0%), respectively, and CPR calculated in 133/186 (71.5%). There was no significant effect of BMI, CRL, or BPD on successful assessment of MCA or CPR. Normograms for MCA PI and CPR revealed no significant relation with CRL or BPD.

Conclusion MCA and CPR assessment is feasible at 12 to 14 weeks. A reference range for MCA Doppler indexes and CPR at 12 to 14 weeks has been established. This may prove helpful in the early evaluation of fetuses identified as at-risk for adverse neonatal outcome.

Keywords
- ► middle cerebral artery
- ► first trimester scan
- ► pulsatility index
- ► peak systolic velocity
- ► cerebroplacental ratio

With the technological advances and the rise in the role of a full fetal anatomic scan at the time of nuchal translucency (NT) assessment,[1,2] there has been an increase in emerging data on various screening markers, particularly those for the early detection of congenital heart defects (CHDs): NT, tricuspid regurgitation, ductus venosus flow, and most recently the cardiac axis.[3–9] Recent studies suggest that the brain sparing effect, first described in CHD by Donofrio et al,[10] may be evident as early as the first trimester in fetuses with CHD. We have previously shown that fetuses with CHD, particularly those with hypoplastic left heart syndrome, may manifest a decrease in head volume as early as the first trimester.[11] This may potentially imply impaired neurodevelopment.

The earliest studies on the fetal cerebral circulation, by Wladimiroff et al in 1986, provided evidence in support of the presence of the brain sparing effect in case of fetal hypoxemia.[12] Since then, several studies have evaluated the fetal circulation, as early as 10 weeks: in the 1990s, Wladimiroff et al evaluated fetal arterial flow velocities[13,14] and fetal heart rate and flow velocity variability;[15] in 2002, Matias et al performed full first trimester fetal hemodynamic evaluation;[16] in 2007, Tongsong et al established the peak

received
November 7, 2017
accepted after revision
May 21, 2018
published online
July 6, 2018

DOI https://doi.org/10.1055/s-0038-1661404.
ISSN 0735-1631.

systolic velocity (PSV) of the middle cerebral artery (MCA) in healthy fetuses between 11 and 22 weeks,[17] and Rujiwetpongstorn and Phupong evaluated Doppler indexes of the MCA in healthy fetuses at 11 to 20 weeks.[18]

The cerebroplacental ratio (CPR) is the ratio of the pulsatility index (PI) of the MCA to the PI of the umbilical artery (UA). It was first described by Gramellini et al in 1992 as a more sensitive predictor of adverse perinatal outcome, at 30 to 41 weeks, with an accuracy of 90% when compared with either the MCA (78.8%) or UA (83.3%).[19] The CPR reflects acute changes in partial pressure of oxygen.[20] In 2003, Baschat and Gembruch reevaluated the CPR in normal fetuses between 20 and 40 weeks of gestation and constructed the reference ranges.[20] To date, we are not aware of the availability of reference values for the CPR in the first trimester. As such, this study was designed to assess the feasibility of visualizing the MCA, establishing the normogram for MCA PI and PSV, and developing CPR normograms at 12 to 14 weeks of gestation in an unselected pregnancy population.

Study Design

This was a prospective cross-sectional study, approved by the Institutional Review Board, on 200 gravidas with spontaneous conception of singleton gestations, presenting for NT assessment between 12w0d and 13w6d at two centers in Lebanon and with an NT < 95th centile for gestational age. All patients were properly dated by an early scan. Maternal body mass index (BMI), fetal crown-rump length (CRL), biparietal diameter (BPD), and NT were measured. At our centers, a full anatomic scan is performed at the time of NT assessment. Fetuses with any structural abnormalities, in utero fetal demise, and those without a confirmed outcome of a healthy neonate were excluded from the analysis. All exams were performed transabdominally by two experienced sonologists using 4 to 8 MHz convex high-resolution probes with two-dimensional and three-dimensional capabilities (GE Voluson E8 ultrasound systems, Kretz, Zimpf, Austria). For the identification of the MCA, the plane of BPD, caudal to the thalamus, was obtained and first trimester cardiac presents, using color Doppler with high-definition flow, were utilized (►**Fig. 1**).

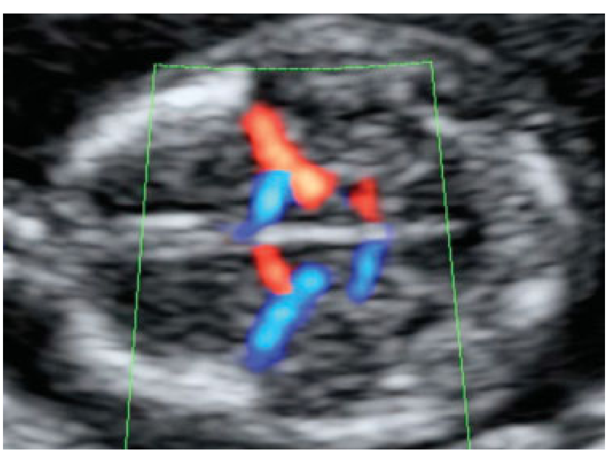

Fig. 1 Circle of Willis.

Subsequently, the MCA PI and PSV were measured at the proximal one-third of the MCA with an angle of insonation of < 10°. The UA was identified, using the same presets and color Doppler with high-definition flow, and the PI was measured in a free loop of cord. We employed the As Low As Reasonably Achievable principle[21] maintaining a thermal index of < 1 and minimizing scanning time with color and pulse wave Doppler to less than 2 minutes as per the American Institute of Ultrasound in Medicine[22] and International Society of Ultrasound in Obstetrics & Gynecology[23] safety recommendations. The CPR was calculated as the ratio of the PI of the MCA to the PI of the UA. The normograms for the MCA PI and CPR were constructed. Regression analysis approach and different polynomial degrees (second and third) were used to study the reference range of the MCA PI and CPR according to CRL and BPD. The normogram for the MCA PSV was determined using crude data and compared with what has been established in a Thai population. Chi-square and *t*-test were utilized. A *p*-value of < 0.05 was considered significant.

Results

A total of 186 fetuses were included in our final analysis (►**Fig. 2**). Maternal and fetal characteristics are summarized in ►**Table 1**. The MCA was successfully visualized in 176/186 (94.6%) of fetuses. The MCA PI and PSV were obtained on 148/186 (79.6%) and 145/186 (78.0%) fetuses, respectively.

There was no significant effect of maternal BMI, fetal CRL, or BPD on successful visualization of the MCA (►**Table 2**). The normogram for the MCA PI in our population was established according to gestational age as well as CRL categories (►**Table 3**). The mean PI values at a gestational age of 12 weeks (2.56) and at 13 weeks (2.37) obtained in this study were comparable with previously published data by Rujiwetpongstorn and Phupong in 2007[18] at a gestational age of 12 weeks (2.55) and at 13 weeks (2.30) with no significant difference ($p = 0.999$ and $p = 0.630$, respectively). The reference range of the MCA PI according to CRL (►**Fig. 3**) and BPD (►**Fig. 4**) was determined. There was no significant relation between MCA PI with CRL ($p = 0.065$) and between MCA PI with BPD ($p = 0.195$), with a best fitted linear regression modeling yield of: MCA PI = 3.541 to 0.017 CRL ($R^2 = 0.023$) and MCA PI = 2.57 to 0.00653.182 to 0.035 BPD ($R^2 = 0.011$), respectively. The normogram for the MCA PSV in our population was established and it was comparable to what has previously been published by Tongsong et al[17] and Rujiwetpongstorn and Phupong[18] (►**Fig. 5**).

The UA was successfully measured and CPR calculated in 133/186 (71.5%) of cases. The normogram for the CPR in our population was established according to the gestational age as well as CRL categories (►**Table 4**), and the reference range of the CPR according to CRL (►**Fig. 6**) and BPD (►**Fig. 7**) was determined. There was no significant effect of BMI, CRL, or BPD on successful assessment of the CPR (►**Table 5**). In addition, there was no significant relation between CPR and CRL ($p = 0.778$), or CPR with BPD ($p = 0.130$), with a best fitted linear regression modeling yield of: CPR = 0.832 to 0.002 CRL ($R^2 = 0.023$) and CPR = 0.285 to 0.031 BPD ($R^2 = 0.130$), respectively.

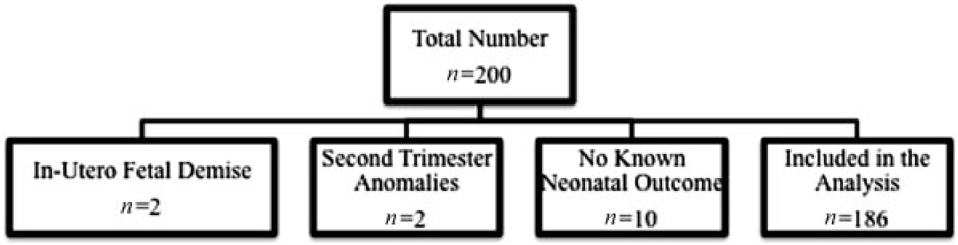

Fig. 2 Flowchart of data collection for fetal inclusion in the study.

Discussion

As our data demonstrate, it is possible to visualize the MCA in 176/186 (94.6%) of cases at the time of NT assessment. There seems to be no impact of maternal BMI, fetal CRL, or BPD on successful visualization, keeping in mind the low BMI in our patient population (mean, 24.5 kg/m^2).

We have been able to establish the normogram for the MCA PI at 12 to 14 weeks in our unselected pregnancy population (►**Table 3**). In addition, we have established the normogram for the MCA PSV and it is comparable to what has already been established by Tongsong et al and Rujiwetpongstorn and Phupong in a Thai population[17,18] (►**Fig. 5**). There is no significant relationship between MCA PI and fetal CRL or BPD. It is important to note that there has been inconsistency in various studies as to where the MCA Doppler indexes are measured: we chose the proximal one-third as did both Tongsong et al and Rujiwetpongstorn and Phupong in a Thai population.[17,18] This was not the case in the second trimester with Baschat and Gembruch.[20]

The CPR was successfully calculated in 133/186 (71.5%) of cases and the normogram established. As with the MCA PI, there was no significant relationship between the CPR and fetal CRL or BPD. This is consistent with what has been shown in the second trimester by Baschat and Gembruch:[20] our data show that the CPR is not constant between 12 and 14 weeks. In contrast to a CPR greater than 1.08 in second trimester normal fetuses,[20] the CPR may be less than 1 at 12 to 14 weeks (►**Table 4**). This may be attributed to the high UA PI in early gestation and the typical absence of end-diastolic flow prior to 13 weeks.[16] By a gestational age of 13 weeks, the 50th centile for the CPR approaches 1 (►**Table 4**). As such, the examiner should be mindful to the fact that the CPR tends to be less than 1 in normal fetuses prior to 13 weeks.

The strength of our study is that it is prospective in nature and we have a large cohort of patients: 186 patients at 12 to 14 weeks with a confirmed outcome of a normal neonate in comparison to prior studies involving first trimester fetuses. The two previous studies in a Thai population included 410 and 149 patients, respectively; however, they were spread out between 11 and 22 weeks.[17,18]

Table 1 Maternal and fetal characteristics

	N	Mean	Standard deviation
Maternal parameters			
BMI (kg/m^2)	186	24.66	4.34
Fetal parameters			
CRL (mm)	186	68.12	7.41
BPD (mm)	186	22.13	2.52
NT (mm)	186	1.70	0.41

Abbreviations: BMI, body mass index; BPD, biparietal diameter; CRL, crown-rump length; GA, gestational age; NT, nuchal translucency.

Table 3 Normogram of calculated MCA PI at the 5th, 10th, 50th, 90th, and 95th percentiles for each gestational age

GA (wk)	MCA PI				
	5th	10th	50th	90th	95th
12	1.00	1.26	2.56	3.40	3.49
13	1.00	1.35	2.37	3.22	3.53
CRL categories					
$<$ 65 mm	0.97	1.07	2.50	3.41	3.72
[65–70] mm	1.39	1.52	2.74	3.41	3.57
[70–75] mm	1.00	1.00	2.47	3.42	3.54
$\geq$ 75 mm	1.03	1.32	2.22	3.14	3.45

Abbreviations: CRL, crown-rump length; GA, gestational age; MCA, middle cerebral artery; PI, pulsatility index.

Table 2 Successful visualization of MCA by maternal and fetal parameters

	MCA not seen			MCA seen			*p*-Value
	N	Mean	Standard deviation	*N*	Mean	Standard deviation	
Maternal BMI	38	24.80	4.85	148	24.62	4.21	0.826
Fetal CRL (mm)	38	67.93	7.37	148	68.17	7.44	0.856
Fetal BPD (mm)	38	21.76	2.60	148	22.22	2.50	0.315

Abbreviations: BMI, body mass index; BPD, biparietal diameter; CRL, crown-rump length; GA, gestational age; MCA, middle cerebral artery.

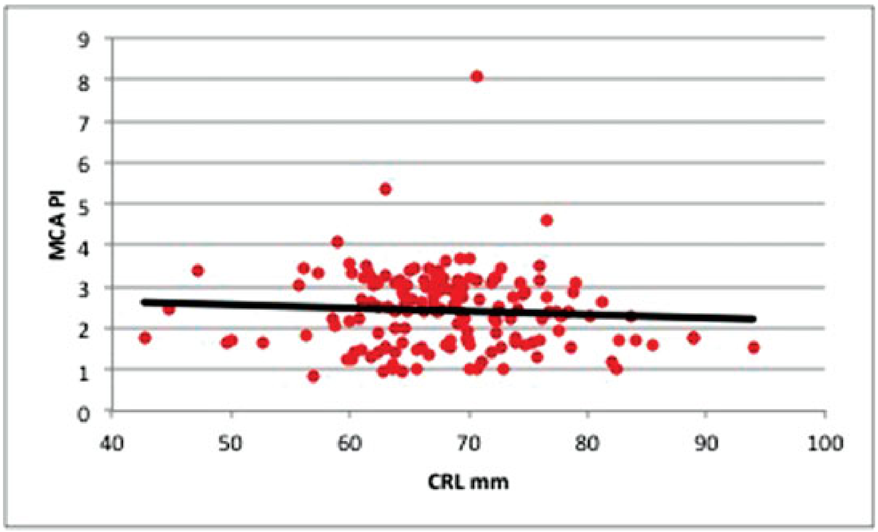

Fig. 3 Regression analysis of the middle cerebral artery (MCA) pulsatility index (PI) by crown-rump length (CRL).

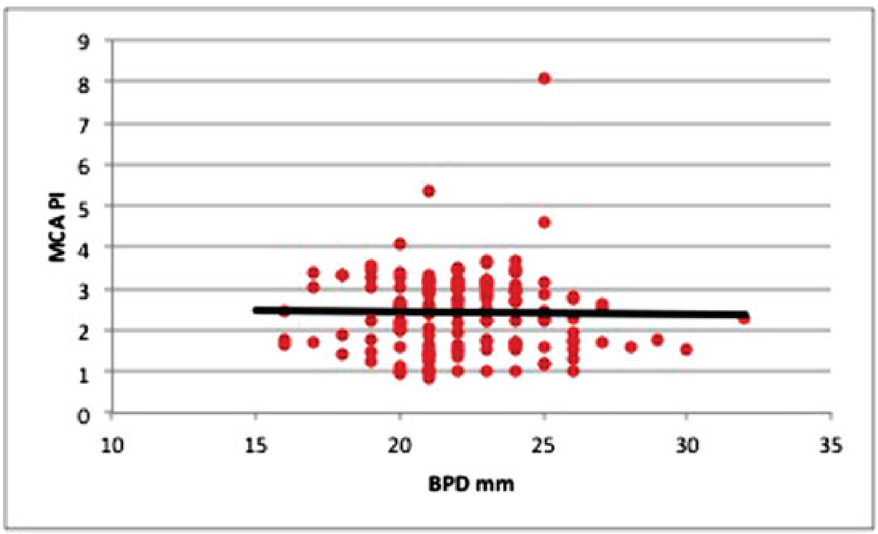

Fig. 4 Regression analysis of the middle cerebral artery (MCA) pulsatility index (PI) by biparietal diameter (BPD).

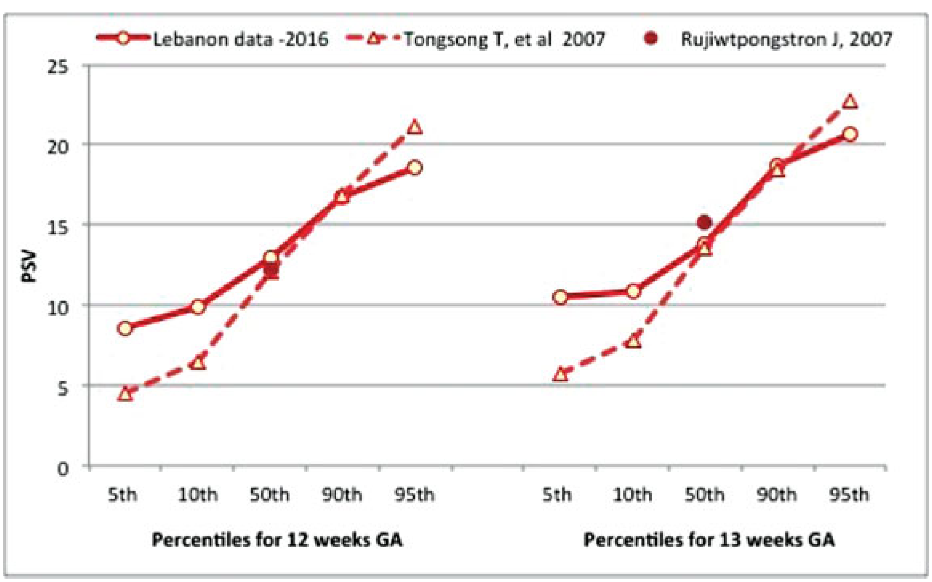

Fig. 5 The normogram for middle cerebral artery (MCA) peak systolic velocity (PSV) by gestational age (GA) in comparison with Tongsong et al and Rujiwetpongstorn and Phupong.

Table 4 Normogram of calculated CPR at the 5th, 10th, 50th, 90th, and 95th percentiles for each gestational age and CRL categories

GA (wk)	CPR				
	5th	10th	50th	90th	95th
12	0.17	0.29	0.81	1.69	1.96
13	0.23	0.35	0.98	1.94	2.23
CRL categories					
$<$ 65 mm	0.15	0.32	0.80	1.81	2.19
[65–70[mm	0.16	0.23	0.92	1.96	2.29
[70–75[mm	0.29	0.36	0.75	1.99	3.17
$\geq$ 75 mm	0.39	0.48	0.98	1.62	1.74

Abbreviations: CPR, cerebroplacental ratio; CRL, crown-rump length; GA, gestational age.

Table 5 Successful calculation of CPR by maternal and fetal parameters

	CPR not calculated			CPR calculated			*p*-Value
	N	Mean	Standard deviation	*N*	Mean	Standard deviation	
Maternal BMI (kg/m^2)	53	24.68	4.57	133	24.65	4.26	0.968
Fetal CRL, mm	53	68.27	7.16	133	68.07	7.53	0.866
Fetal BPD, mm	53	22.04	2.54	133	22.16	2.52	0.781

Abbreviations: BMI, body mass index; BPD, biparietal diameter; CPR, cerebroplacental ratio; CRL, crown-rump length.

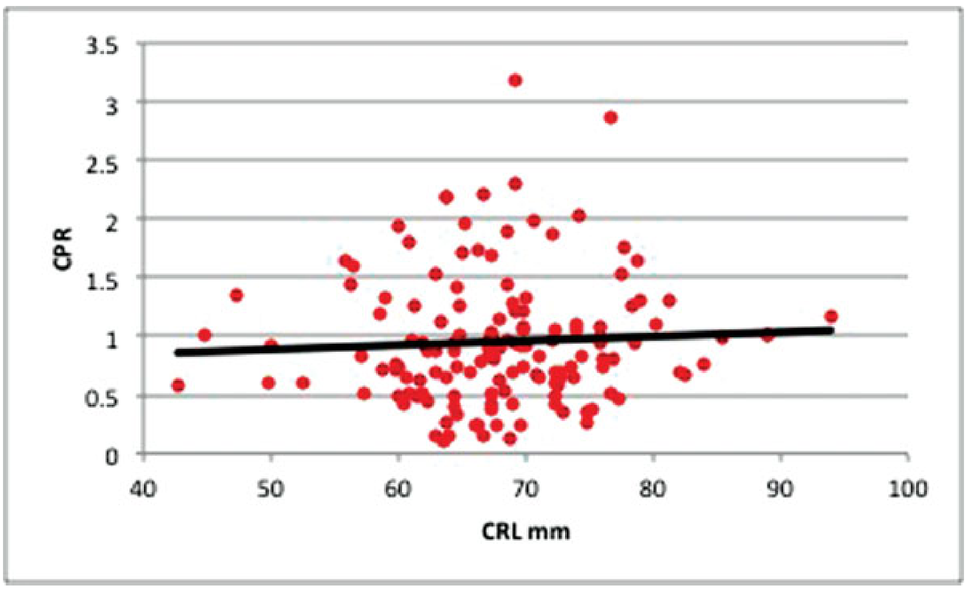

Fig. 6 Regression analysis of cerebroplacental ratio (CPR) by crown-rump length (CRL).

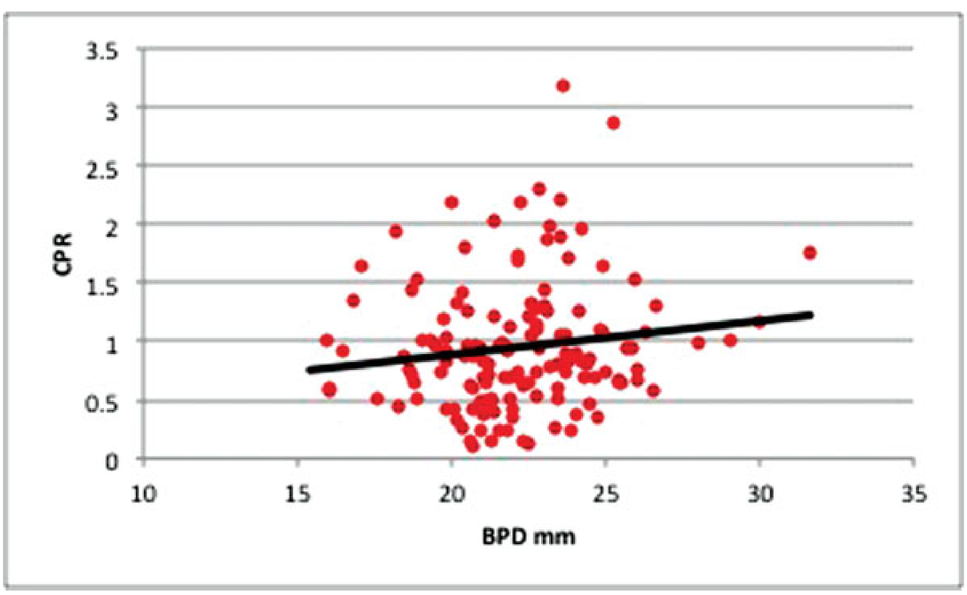

Fig. 7 Regression analysis of cerebroplacental ratio (CPR) by biparietal diameter (BPD).

In addition, our data are further validated by the fact that with our larger numbers, the results in our unselected Lebanese population are comparable to what has already been established with respect to both the MCA PI and PSV in a Thai population. It is noteworthy that both studies from Thailand, as ours, were cross-sectional studies.[17,18]

Our study has several limitations. Given Doppler indexes at the proximal one-third of the MCA are less likely to be affected by fetal behavioral status as described by Clerici et al in 2002,[24] we chose to measure the MCA Doppler indexes at the proximal one-third of the MCA, an area where they may be lower than at the middle and distal third.[25] Furthermore, we did not evaluate maternal uterine artery Doppler indexes and their potential effect on fetal perfusion and the CPR.

In conclusion, MCA evaluation is feasible at the time of NT assessment. To our knowledge, our study is the first to provide a reference range for first trimester CPR at 12 to 14 weeks. Having established normograms for MCA Doppler indexes and CPR at 12 to 14 weeks may prove helpful, when indicated, in the early assessment of at-risk fetuses identified by abnormal uterine artery Doppler studies, maternal risk factors, those at risk for anemia, growth restriction, and impending demise, among others. Larger prospective studies are needed to examine the potential role of the MCA Doppler indexes and CPR as first trimester modalities in the evaluation of fetuses at risk for adverse neonatal outcome.

Note

This article has been presented as two oral abstract presentations at the AIUM Annual Convention in Orlando, Florida, in March 2017.

Conflict of Interest

None.

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