Fetal Diagnosis and Therapy

Original Paper

Fetal Diagn Ther
DOI: 10.1159/000508366

Received: November 20, 2019
Accepted: April 26, 2020
Published online: July 14, 2020

Prescriptive Reference Standards of Third-Trimester Cerebroplacental Ratio and Its Physiological Determinants

Marta Rial-Crestelo[a] Laura Garcia-Otero[b] Annalisa Cancemi[b] Mariella Giannone[b] Elena Escazzocchio[c] Alex Biterna[d] Elena Ferriols[e] Jose Luis Hernandez[e] Marek Lubusky[f] Veronika Kolarova[f] Ladislav Krofta[g] Jiri Vojtêch[h] Eyal Zohav[i] Karina Krajden[j] Rogelio Cruz-Martinez[k] Monica Cruz-Lemini[k] Mauro Parra-Cordero[l] Pamela Socias[m] Fàtima Crispi[n] Marta Lopez[a] Eduard Gratacós[a] Francesc Figueras[a]
on behalf of the Ratio 37 study group

[a]Hospital Clinic Barcelona, Fetal Medicine Unit, Fetal Medicine Research Center, BCNatal–Barcelona Center for Maternal-Fetal and Neonatal Medicine (Hospital Clínic and Hospital San Joan de Deu), Barcelona, Spain; [b]Fetal Medicine Unit Fetal Medicine Research Center, BCNatal–Barcelona Center for Maternal-Fetal and Neonatal Medicine (Hospital Clínic and Hospital San Joan de Deu), Barcelona, Spain; [c]Atenció a la Salut Sexual i Reproductiva (ASSIR) de Barcelona ciutat, Institut Catala de la Salut, Barcelona, Spain; [d]Obstetrics and Gynecology Institut Catala de la Salut, Atencio Primaria Barcelona Ciutat, Barcelona, Spain; [e]Obstetrics and Gynecology Consorci Parc de Salut Mar, Hospital del Mar, Barcelona, Spain; [f]Department of Obstetrics and Gynecology, Palacky University Olomouc, Faculty of Medicine and Dentistry, University Hospital Olomouc, Olomouc, Czech Republic; [g]Obstetrics and Gynecology, Institute for the Care of Mother and Child, Prague, Czech Republic; [h]Center of Fetal Medicine, Institute for the Care of Mother and Child, Prague, Czech Republic; [i]Department of Obstetrics and Gynecology, Affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [j]Wolfson Medical Center, Ultrasound Unit, Fetal Neurology Clinic, Holon, Israel; [k]Fetal Medicine Research Center, Fetal Medicine Mexico, Querétaro, Mexico; [l]Fetal Medicine Unit, Hospital Clínico Universidad de Chile, Santiago de Chile, Chile; [m]Obstetrics and Gynecology Fetal Medicine Unit, University of Chile Hospital, Santiago de Chile, Chile; [n]Maternal-Fetal Medicine BCNatal-Barcelona Center for Maternal-Fetal and Neonatal Medicine (Hospitals Clínic and Sant Joan de Déu), IDIBAPS, Barcelona University, Centre for Biomedical Research on Rare Diseases (CIBER-ER), Barcelona, Spain

Keywords
Cerebroplacental ratio · Color Doppler ultrasonography · Doppler ultrasound · Fetal growth restriction · Normality ranges

Abstract
Objective: To construct valid reference standards reflecting optimal cerebroplacental ratio and to explore its physiological determinants. ***Methods:*** A cohort of 391 low-risk pregnancies of singleton pregnancies of nonmalformed fetuses without maternal medical conditions and with normal perinatal outcomes was created. Doppler measurements of the middle cerebral artery and umbilical artery were performed at 24–42 weeks. Reference standards were produced, and the influence of physiological determinants was explored by nonparametric quantile regression. The derived standards were validated in a cohort of 200 low-risk pregnancies. ***Results:*** Maternal body mass index was significantly associated with the 5th centile of the cerebroplacental ratio. For each

karger@karger.com
www.karger.com/fdt

Francesc Figueras
Fetal Medicine Department, Hospital Clinic, University of Barcelona
1 Sabino de Arana
ES–08028 Barcelona (Spain)
ffiguera@clinic.cat

additional unit of body mass index, the 5th centile was on average 0.014 lower. The derived 5th, 10th, and 50th centiles selected in the validation cohort were 5, 9.5, and 51% of the measurements. ***Conclusions:*** This study provides methodologically sound prescriptive standards and suggests that maternal body mass index is a determinant of a cutoff commonly used for decision-making.

Introduction

The use of Doppler to assess placental function and the risk of adverse perinatal outcomes is a benchmark of modern obstetrics [1]. Placental disease and cerebral vascular redistribution can be correctly assessed by the umbilical artery (UA) and middle cerebral artery (MCA) Doppler, respectively [2, 3]. Because of increased impedance in the placental vasculature in combination with a decrease in cerebral resistance secondary to vasodilation, the ratio between the MCA and the UA Doppler (the cerebroplacental ratio [CPR]) is decreased even when the UA and MCA pulsatility indices (PIs) are still within normal ranges. Consistently, animal models have demonstrated that the CPR correlates better with hypoxia than its individual components [4], making this parameter a good candidate for early identification of placental insufficiency. Indeed, there are 4 systematic reviews and meta-analyses showing that this parameter captures well the perinatal risks of placental insufficiency [5–8].

The technicalities of Doppler assessment of the UA and the MCA have been standardized [9]. However, many ranges of normality have been described and the studies that have developed them are not entirely well designed, which explains the large heterogeneity between them in terms of reference values. In particular, in the case of CPR, a total of 4 reference ranges [10–13] have been published, with little concordance between them. Recently, a systematic review has evaluated the quality and design of these reference ranges by means of quality criteria of 24 predefined items, concluding that the largest deficits in all studies were the lack of quality control measures and the absence of blinding. Regarding the reporting methods, most of the studies did not report the experience of the operators or the number of measures taken by them, did not calculate the size of the sample needed for the study, and did not report information about the recruitment period [14].

In this study, we had a triple aim: producing reference standards reflecting the optimal cerebroplacental ratio, validating them in a cohort of low-risk pregnancies, and exploring the physiological maternal and fetal determinants of this parameter.

Materials and Methods

Study Population

Construction Sample

A cohort was prospectively created of consecutive pregnancies without medical conditions attended for 19–23-week routine scan at a referral university hospital (Barcelona Hospital Clinic) between September 2015 and October 2017. Inclusion criteria were singleton, nonmalformed, nonsmoking, and healthy pregnancies (without any maternal medical condition). After acceptance to participate, each woman was scheduled a single Doppler measurement between 24 and 41 weeks specifically for research purposes, until completion of the required sample size. Women were excluded if after recruitment any of the following criteria were met: congenital malformation, chromosomopathy, infection, pregnancy complication (hypertension defined as SBP ≥140 mm Hg and/or DBP ≥90 mm Hg, gestational diabetes, and metrorrhagia), or adverse perinatal outcomes (perinatal death, birth weight below the 10th centile according to local standards [15], preterm delivery [<37 weeks], neonatal acidosis [arterial cord blood pH <7.15], or admission to the neonatal intensive care unit [NICU]). Patients with history of pre-eclampsia, fetal growth restriction (FGR), or stillbirth were excluded. All pregnancies were dated according to the 1st-trimester crown-rump length measurement [16]. All women gave written consent to participate.

External Validation Sample

For external validation, a subsample of the Ratio37 study [17] was randomly selected (20 per each gestational age between 32 and 41 weeks) with stratification by participating centers: Hospital Clinic (Barcelona), Lis Hospital for Women (Tel Aviv University), University Hospital Olomouc (Czech Republic), University Hospital of Chile, and Hospital de Especialidades del Niño y la Mujer (Mexico). The Ratio37 trial is an ongoing randomized, open-label, multicenter, controlled study in which women with low-risk pregnancies are recruited at 20 weeks of pregnancy and the measurements of the UA and MCA are performed at the 37th week. This study was accepted by the Clinical Research Ethics Committee of Hospital Clinic Barcelona on May 23, 2016 (RCT01ABRIL, HCB/2016/0108; Trial Registration Number: NCT02907242). Images of the Doppler measurements are systematically stored in DICOM (Digital Imaging and Communications in Medicine) format and subjected to quality audits.

Measurements

All Doppler ultrasound examinations were performed by using 3 certified sonographers blinded to the results using either a General Electric Voluson E8 or Siemens Sonoline Antares. For both the construction sample and the validation samples, Doppler measurements were performed adhering to the recommendation by the International Society of Obstetrics and Gynecology (ISUOG) [9]. Doppler measures were obtained in the absence of fetal movements and with voluntarily suspended maternal breathing. Doppler parameters were measured automatically from three or more

Table 1. Baseline characteristics of the 391 women in the construction sample and the 200 patients of the validation sample

Age, years	32.5 (4.7) [19–42]	32 (5.03) [18–45]
Weight, kg	62.3 (10.6) [40–101]	63 (10.5) [55–109]
Height, cm	162 (7) [145–184]	162.6 (6.7) [144–181]
BMI at booking	23.5 (3.8) [18–36]	23.8 (3.8) [17–40]
Ethnicity		
White European	261 (66.8%)	121 (60.5%)
Latin American	77 (19.7%)	54 (27%)
Others	53 (13.6%)	25 (12.5%)
Low maternal class	85 (21.7%)	44 (22%)
Smoking at booking	0	0
Nulliparity	200 (51.2%)	101 (50.5%)
Gestational age at birth, weeks	39.98 (1.04) [36.57–42.29]	40.1 (0.9) [37–42]
Birthweight, g	3,424 (367.5) [2,440–4,360]	3,489.7 (346.9) [2,490–4,460]
Mode of delivery		
Spontaneous delivery	284 (72.7%)	136 (68%)
Instrumental vaginal delivery	42 (10.7%)	16 (8%)
Cesarean section	65 (16.7%)	48 (24%)
Male gender	192 (49.1%)	107 (53.5%)
Fetal distress requiring emergent delivery	16 (4.1%)	10 (5%)

The values are presented as mean (SD) [range] or *n* (%).

consecutively similar waveforms, with the angle of insonation as close to 0° as possible. UA PI was measured from a free-floating cord loop. MCA PI was measured in a transversal view of the fetal head, at the level of its origin from the circle of Willis.

Statistical Analysis

Sample size estimation [18] was performed to estimate the 5th quantile, with 95% confidence interval and with 85% of relative margin of precision when compared with the 90% reference range, resulting in 338 women uniformly distributed across the gestational age range (24–41 weeks). To calculate the simple size, we used the assumptions of linearity (the relationship between gestational age and the observations can be expressed by a polynomial function) and normality (in each gestational week, the observations follow a normal distribution). Both assumptions were checked in our analysis. As the aim was to derive prescriptive standards (reflecting optimal CPR), we accounted for a 25% exclusion due to subsequent pregnancy complication or abnormal perinatal outcomes, resulting in a minimum of 450 women (25 per each week).

Both the reference standards and the analysis of physiological determinants (gestational age, maternal BMI at booking, maternal age, nulliparity, and fetal gender) of CPR were performed using quantile regression, as described by Wei et al. [19]. Quantile regression estimates the distribution directly by fitting a function to each chosen quantile using linear programming, without distributional assumptions. In addition, quantile regression is more robust against the influence of outliers in the data. The estimated quantiles (5th, 10th, 50th, and 95th) were smoothed by polynomial functions of gestational age. The degree of the polynomial was determined by minimizing the Akaike Information Criteria (AIC) of the model. The models were checked by the residual analysis. Hypotheses on the overall importance of covariates' coefficient were tested by Student's *t* test. To evaluate the goodness of fit of the derived quantiles in the validation sample, the one-sample χ^2 test was performed to assess whether the observed frequency of observations below the 5th, 10th, 50th, 90th, and 95th centiles differed from the expected frequencies of 5, 10, 50, 90, and 95% (a p value >0.05 refutes the alternative hypothesis of a difference between observed and expected frequencies). For all the statistical analysis, R version 2.15.1 (The R Foundation for Statistical Computing; quantreg package 5.05) was used.

Results

A total of 526 women met the inclusion criteria. Of them, 25 were excluded because of pregnancy complications (14 gestational diabetes, 9 hypertensive disorders, and 2 uterine bleeding), 41 for a birth weight below the 10th centile, 13 for preterm delivery, and 56 for neonatal acidosis, leaving 391 women for the analysis (uniformly distributed between 24 and 41 weeks). For the validation sample, 200 women were selected (20 per each gestational age between 32 and 41 weeks). Table 1 shows the baseline characteristics of the included women.

Table 2 shows the influence of the physiological determinants on each of the analyzed CPR quantiles. Of note, maternal BMI was significantly and negatively associated with the 5th centile. For each additional unit of BMI, the 5th centile was 0.014 lower. For details about the influence of the physiological determinants on the MCA and

Table 2. Influence of physiological determinants on the CPR quantiles

	Coefficient	SE	*t* value	*p* value
5th centile				
Constant	−0.478	0.489	−0.978	0.328
GA	0.131	0.034	3.872	<0.001
GA^2	−0.002	0.001	−3.430	0.001
BMI	−0.014	0.006	−2.138	0.033
Age	−0.002	0.005	−0.352	0.725
Nulliparity	−0.025	0.048	−0.525	0.600
Gender	−0.009	0.045	−0.197	0.844
10th centile				
Constant	−1.371	0.495	−2.771	0.006
GA	0.184	0.034	5.431	<0.001
GA^2	−0.003	0.001	−4.708	<0.001
BMI	−0.008	0.006	−1.384	0.167
Age	0.00002	0.005	0.003	0.997
Nulliparity	0.006	0.055	0.117	0.907
Gender	−0.037	0.055	−0.677	0.499
50th centile				
Constant	−2.413	0.466	−5.181	<0.001
GA	0.256	0.029	8.935	<0.001
GA^2	−0.004	0.0005	−7.713	<0.001
BMI	0.006	0.007	0.843	0.400
Age	−0.002	0.005	−0.337	0.736
Nulliparity	0.045	0.046	0.963	0.336
Gender	−0.021	0.045	−0.465	0.642
90th centile				
Constant	−3.379	0.782	−4.323	<0.001
GA	0.376	0.055	6.843	<0.001
GA^2	−0.006	0.001	−5.620	<0.001
BMI	−0.002	0.010	−0.160	0.873
Age	−0.010	0.008	−1.215	0.225
Nulliparity	−0.046	0.074	−0.628	0.531
Gender	0.021	0.074	0.291	0.771
95th centile				
Constant	−3.025	0.979	−3.090	0.002
GA	0.355	0.061	5.795	<0.001
GA^2	−0.005	0.001	−4.837	<0.001
BMI	−0.014	0.010	−1.400	0.162
Age	0.002	0.009	0.202	0.840
Nulliparity	−0.074	0.091	−0.809	0.419
Gender	0.062	0.086	0.723	0.470

CPR, cerebroplacental ratio; GA, gestational age.

Table 3. Coefficients for formulas for each of the studied quantiles (exact weeks)

	Coefficient
5th centile	
Constant	−0.541
GA	0.106
GA^2	−0.002
10th centile	
Constant	−1.321
GA	0.165
GA^2	−0.002
50th centile	
Constant	−2.554
GA	0.274
GA^2	−0.004
90th centile	
Constant	−3.996
GA	0.400
GA^2	−0.006
95th centile	
Constant	−3.483
GA	0.365
GA^2	−0.005

GA, gestational age.

UA, see online suppl. Tables 1 and 2 (for all online suppl. material, see www.karger.com/doi/10.1159/000508366).

Table 3 shows the formulas for each of the studied quantiles. Of note, quadratic models provided the best fit (by minimizing AIC) for all the analyzed quantiles. Table 4 details the derived quantiles against gestational age. Online suppl. Table 3 details the reference ranges for the MCA and UA.

The results in the validation sample are shown in Figure 1. Of note, of the 200 measurements, 10 (5%) were below the 5th centile ($p = 1$), 19 (9.5%) below the 10th centile ($p = 0.81$), 102 (51%) below the 50th centile ($p = 0.78$), 184 (92%) below the 90th centile ($p = 0.35$), and 191 (95.5%) below the 95th centile ($p = 0.78$).

Discussion

The use of normal ranges and thresholds is essential to interpret results objectively. In the case of fetal Doppler parameters, this interpretation may trigger delivery. A low CPR is associated with a range of adverse pregnancy outcomes, including stillbirth, admission to the NICU, acidosis, composite neonatal morbidity, and emergency operative birth for intrapartum fetal compromise [5–8]. Recommendations based on expert consensus and some professional bodies now incorporate consideration of the CPR when making decisions regarding appropriate surveillance and/or timing of birth in cases of late-onset small-for-gestational age (SGA) or FGR [20, 21]. Thus, accurately defining the cutoff for abnormal CPR is key in clinical practice. Over the last 20 years, some reference ranges have been published [10–13] (summarized in Ta-

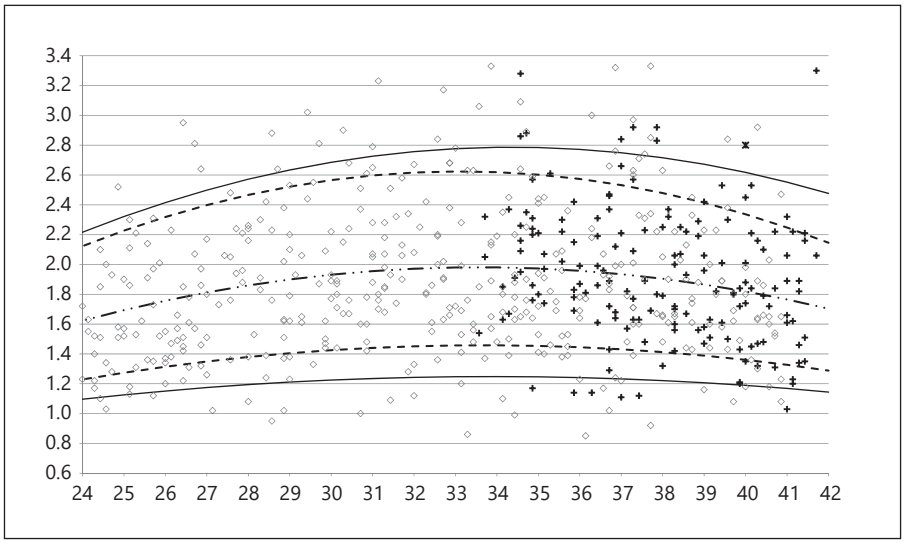

Fig. 1. CPR measurements in the validation sample (n = 200) plotted against the reference ranges: ——, p5 and p95; -----, p10 and p90; — ·· —, p50. Diamonds: construction cohort; crosses: validation cohort.

ble 5), all 4 with design deficits according to a recent systematic review that checked their quality [14]. The best of these studies [11] methodologically only met 2/3 of the quality criteria. This finding sparked our study to derive reference ranges fulfilling the quality criteria on the study design and reporting and statistical methods. More recently, a study has been published [22] on a large cohort of pregnancies undergoing routine screening (nonselected population) at 20^0–22^6, 31^0–33^6, 35^0–36^6, and 41^0–41^6, and references were derived for the whole range of gestational ages between 20 and 41 weeks.

One aspect that is not considered as a quality criterion in the systematic review but that has key importance is external validity assessment. Before considering whether to use a reference range, it is required that its performance has been evaluated in datasets that were not used to construct the model, that is, external validation. Externally validating a reference range in a different geographical setting is a good measure of its generalizability and transportability. We opted to externally validate our ranges in a subsample of the ongoing Ratio37 study [17], which was designed as a pragmatic trial [23], as the main objective is to test the real-setting effectiveness of a strategy of labor induction at 37 weeks of low-risk pregnancies with abnormal CPR, in broad patient groups from different practices and practitioners. We found in this validation that our reference 5th and 10th standard accurately selected 5 and 10% of the measurements.

One worth-discussing finding of our study is that the 5th centile is negatively influenced by maternal body mass index. The magnitude of this effect is not negligible: at the 37th week, the 5th centile would be 1.39, 1.32, and 1.25 for women with a BMI of 20, 25, and 30, respectively. This finding is not explained by technical difficulties encountered in women with high BMI since excessive pressure on the fetal head is likely to increase pulsatility rather than lowering it [24, 25]. One can speculate that in obese women, the described proinflammatory systemic environment [25, 26] leads to placental involvement. A recent study published in 2015 has found that maternal

Table 4. Reference ranges of CPR by exact weeks

	5th centile	10th centile	50th centile	90th centile	95th centile
24	1.10	1.23	1.62	2.12	2.22
25	1.13	1.27	1.69	2.23	2.32
26	1.15	1.31	1.76	2.32	2.42
27	1.17	1.35	1.81	2.40	2.50
28	1.19	1.38	1.86	2.47	2.57
29	1.21	1.40	1.90	2.52	2.63
30	1.22	1.43	1.93	2.57	2.69
31	1.24	1.44	1.96	2.60	2.73
32	1.24	1.45	1.97	2.62	2.76
33	1.25	1.46	1.98	2.62	2.78
34	1.25	1.46	1.98	2.62	2.79
35	1.25	1.45	1.97	2.60	2.78
36	1.24	1.45	1.96	2.57	2.77
37	1.23	1.43	1.94	2.53	2.75
38	1.22	1.41	1.90	2.48	2.72
39	1.21	1.39	1.87	2.41	2.67
40	1.19	1.36	1.82	2.34	2.62
41	1.17	1.33	1.77	2.25	2.55
42	1.14	1.29	1.70	2.15	2.48

CPR, cerebroplacental ratio.

Table 5. Summary of published normograms of CPR

Study	Kurmanavicius et al. [13]	Baschat and Gembruch [10]	Ebbing et al. [11]	Morales-Roselló et al. [12]	Ciobanu et al. [22]	Current
Year	1997	2003	2007	2014	2019	2019
Country	Switzerland	Germany	Norway	Spain	UK	Spain + multicentric validation
Design	Cross-sectional	Cross-sectional	Longitudinal	Cross-sectional	Cross-sectional	Cross-sectional
N	1,675	306	161	2,323	72,417	340
Scans, *n*	1,675	306	566	2,323	72,417	340
Study period	NR	NR	NR	NR	NR	25 months
Dating	CRL at 1st trimester	Scan before 20 weeks	Head biometry at 17–20 weeks	CRL at 1st trimester	CRL at 1st trimester	CRL at 1st trimester
GA uniformly distributed	No	No	Yes	No	No (4 periods)	Yes
Population	Unselected population	Patients referred for fetal growth assessment	Low risk; gestational complications not excluded	Unselected population	Unselected population	Low risk with normal outcomes
Methodology	Least squares linear regression of mean and SD	Least squares linear regression of mean	Multilevel linear regression	Quantile regression	Least squares linear regression of mean and SD	Quantile regression
MCA portion	Proximal	Distal	Proximal	Proximal	Not reported	Proximal
Validation	No	No	No	No	No	Yes
5th PI centile at different gestational ages	24 NR[a]	1.17	1.16	1.12	1,12	1.10
	28 NR[a]	1.28	1.47	1.23	1.34	1.19
	32 NR[a]	1.24	1.64	1.26	1.44	1.24
	36 NR[a]	1.26	1.55	1.20	1.35	1.24
	40 NR[a]	1.08	NR	1.06	1.09	1.19

CPR, cerebroplacental ratio; CRL, crown-rump length; NR, not reported; MCA, middle cerebral artery; GA, gestational age; PI, pulsatility index. [a] Only resistance indices reported.

obesity is associated with elevated resistance indices in the UA [27]. Consistently, we also found that the effect of high BMI was more pronounced in the umbilical than in the MCA (online suppl. Table 2). A recent study on 72,417 women that underwent a routine scan (not specifically for the purpose of constructing Doppler ranges) reported that BMI >36.5 kg/m^2 increased their CPR p50 values by 0.0482 *z*-values. Translated into natural values, if the overall p50 at the 37th week in their study is 1.894, it would be 2.11 in those with BMI >36.5 kg/m^2. They did not explore the effect of BMI on the thresholds commonly used in clinical practice. It may happen that the effect on the median differs from the effect on the p5 or p10. Other differences between their population and ours are that they did not exclude pregnancies with medical conditions and that the baseline BMI in their series is higher than that in the current study (mean 26.3 at 20–22 weeks vs. 23.5 at booking in the current series). Therefore, while their series is more descriptive (representing references), the current study is more prescriptive (representing standards). A previous study on the maternal physiological determinants of the UA and MCA Doppler that included 34,773 non-SGA pregnancies evaluated between 30^{+0} and 37^{+6} failed to find any effect of maternal weight or height on the median values [28]. Whether BMI-adjusted CPR cutoffs improved the prediction of adverse perinatal outcomes has not been explored. It further adds to the discussion of whether in obese women we should use the nonobese range and interpret the lower values in obese women as indicative of their underlying pathology.

The strengths of our study are that they fulfill most of the methodological quality criteria described elsewhere [14]. In addition, the fact that the CPR cutoffs have been validated in a multicenter sample assures generalizability. Another strong point of our references is that they are fully prescriptive, that is, by only including low-risk pregnancies with normal perinatal outcomes, they reflect which should be the CPR under optimal conditions rather than simply describing how these values are distributed in pregnancy. As for the limitations of our study, it should be acknowledged that we have only externally validated our CPR thresholds in pregnancies beyond 32 weeks. However, it is only near term when the CPR is clinically used for decision-making.

In conclusion, this study provides methodologically sound prescriptive standards and suggests that maternal body mass index is a determinant of the cutoff that is commonly used for clinical decisions.

Acknowledgements

The construction of the normality scale for the cerebroplacental ratio was supported by the Erasmus + Program of the European Union (Framework Agreement No. 2013-0040). The external validation sample was constructed thanks to the Ratio37 team.

Statement of Ethics

Our research complies with the guidelines for human studies, and the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Local ethical committee approval was obtained for this research. This study was accepted by the Clinical Research Ethics Committee of Hospital Clinic Barcelona on May 23, 2016 (RCT01ABRIL, HCB/2016/0108; Trial Registration Number: NCT02907242). Written consents by the patients were obtained.

Conflict of Interest Statement

The authors report no conflicts of interest.

Funding Sources

The authors did not receive any funding.

Author Contributions

M.R.-C. and F.F. prepared the manuscript. All authors contributed to the conception of the study and were involved in amendment and approved the final manuscript.

References

1 Figueras F, Gardosi J. Intrauterine growth restriction: new concepts in antenatal surveillance, diagnosis, and management. Am J Obstet Gynecol. 2011;204(4):288–300.
2 Simonazzi G, Curti A, Cattani L, Rizzo N, Pilu G. Outcome of severe placental insufficiency with abnormal umbilical artery Doppler prior to fetal viability. BJOG An Int J Obstet Gynaecol. 2013;120(6):754–7.
3 Hernandez-Andrade E, Serralde JA, Cruz-Martinez R. Can anomalies of fetal brain circulation be useful in the management of growth restricted fetuses? Prenat Diagn. 2012;32(2):103–12.
4 Arbeille P, Maulik D, Fignon A, Stale H, Berson M, Bodard S, et al. Assessment of the fetal PO2 changes by cerebral and umbilical Doppler on lamb fetuses during acute hypoxia. Ultrasound Med Biol. 1995;21(7):861–70.
5 Nassr AA, Abdelmagied AM, Shazly SA. Fetal cerebro-placental ratio and adverse perinatal outcome: systematic review and meta-analysis of the association and diagnostic performance. J Perinat Med. 2016;44(2):249–56.
6 Dunn L, Sherrell H, Kumar S. Review: systematic review of the utility of the fetal cerebroplacental ratio measured at term for the prediction of adverse perinatal outcome. Placenta. 2017;54:68–75.
7 Schreurs CA, de Boer MA, Heymans MW, Schoonmade LJ, Bossuyt PMM, Mol BWJ, et al. Prognostic accuracy of cerebroplacental ratio and middle cerebral artery Doppler for adverse perinatal outcomes: a systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018;51:313–22.
8 Conde-Agudelo A, Villar J, Kennedy SH, Papageorghiou AT. Predictive accuracy of cerebroplacental ratio for adverse perinatal and neurodevelopmental outcomes in suspected fetal growth restriction: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018;52(4):430–41.
9 Bhide A, Acharya G, Bilardo C, Cafici D, Hernandez Andrade E, Kalache K, et al. ISUOG practice guidelines: use of Doppler ultrasonography in obstetrics. Ultrasound Obstet Gynecol. 2013;41(2):233–9.
10 Baschat AA, Gembruch U. The cerebroplacental Doppler ratio revisited. Ultrasound Obstet Gynecol. 2003;21(2):124–7.
11 Ebbing C, Rasmussen S, Kiserud T. Middle cerebral artery blood flow velocities and pulsatility index and the cerebroplacental pulsatility ratio: longitudinal reference ranges and terms for serial measurements. Ultrasound Obstet Gynecol. 2007;30(3):287–96.
12 Morales-Roselló J, Khalil A, Morlando M, Hervás-Marín D, Perales-Marín A. Doppler reference values of the fetal vertebral and middle cerebral arteries, at 19–41 weeks gestation. J Matern Fetal Neonatal Med. 2015;28(3):338–43.
13 Kurmanavicius J, Florio I, Wisser J, Hebisch G, Zimmermann R, Müller R, et al. Reference resistance indices of the umbilical, fetal middle cerebral and uterine arteries at 24–42 weeks of gestation. Ultrasound Obstet Gynecol. 1997;...

18 Bellera CA, Hanley JA. A method is presented to plan the required sample size when estimating regression-based reference limits. J Clin Epidemiol. 2007;60(6):610–5.
19 Wei Y, Pere A, Koenker R, He X. Quantile regression methods for reference growth charts. Stat Med. 2006;25(8):1369–82.
20 Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol. 2016;48(3):333–9.
21 McCowan LM, Figueras F, Anderson NH. Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy. Am J Obstet Gynecol. 2018;218(2S):S855–68.
22 Ciobanu A, Wright A, Syngelaki A, Wright D, Akolekar R, Nicolaides KH. Fetal Medicine Foundation reference ranges for umbilical artery and middle cerebral artery pulsatility index and cerebroplacental ratio. Ultrasound Obstet Gynecol. 2019;53(4):465–72.
23 Roland M, Torgerson DJ. Understanding controlled trials: what are pragmatic trials? BMJ. 1998;316:285.
24 Alpert Y, Ben-Moshe B, Shvalb N, Piura E, Tepper R. The effect of the pressure exerted on the maternal abdominal wall by the US probe on fetal MCA peak systolic velocity. Ultraschall Med. 2017;38(1):44–50.
25 Howell KR, Powell TL. Effects of maternal obesity on placental function and fetal development. Reproduction. 2017;153(3):R97.
26 Hrolfsdottir L, Schalkwijk CG, Birgisdottir BE, Gunnarsdottir I, Maslova E, Granström C, et al. Maternal diet, gestational weight gain, and inflammatory markers during pregnancy. Obesity. 2016;24(10):2133–9.
27 Sarno L, Maruotti GM, Saccone G, Morlando M, Sirico A, Martinelli P. Maternal body mass index influences umbilical artery Doppler velocimetry in physiologic pregnancies. Prenat Diagn. 2015;35(2):125–8.
28 Akolekar R, Sarno L, Wright A, Wright D, Nicolaides KH. Fetal middle cerebral artery and umbilical artery pulsatility index: effects of maternal characteristics and medical history. Ultrasound Obstet Gynecol. 2015;45(4):402–8.