

Reference ranges for Doppler indices of umbilical and middle cerebral arteries and cerebroplacental ratio: a systematic review

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ABSTRACT

OBJECTIVES: To assess studies reporting reference ranges for Doppler indices of umbilical artery (UA), middle cerebral artery (MCA) and cerebroplacental ratio (CPR), using a set of predefined methodological quality criteria for study design, statistical analysis and reporting methods.

METHODS: A systematic review of observational studies whose primary aim was to create reference ranges for Doppler indices of UA, MCA, and CPR in fetuses from singleton gestations was performed in MEDLINE, EMBASE, CINAHL, and Web of Science (all from inception to December 31, 2016), and references of retrieved articles. Two authors independently selected studies, assessed the risk of bias, and extracted the data. Studies were scored against a predefined set of independently agreed methodological criteria and an overall quality score was assigned to each study. Linear multiple regression analysis between quality scores and study characteristics was performed.

RESULTS: Thirty-eight studies met the inclusion criteria. The highest potential for bias was noted in the following fields: 'Ultrasound quality control measures', where only two studies demonstrated a comprehensive quality assurance strategy; 'Sonographers experience', where no study of CPR clearly reported the experience or training of the sonographers while only three studies of UA Doppler and four of MCA Doppler did; and "Blinding of measurements", in which only one study of UA Doppler reported that sonographers were blinded to the measurement recorded during the examination. Sample size estimations were present in only seven studies. No predictors of quality were found on multiple regression analysis. Reference ranges varied significantly with important clinical implications on what is considered normal or abnormal, even when restricting the analysis to the highest scoring studies.

CONCLUSIONS: There is considerable methodological heterogeneity in studies reporting reference ranges for Doppler indices of UA, MCA and CPR, and the resulting references have important implications for clinical practice. There is a need for the standardization of methodologies for Doppler velocimetry and for the development of reference standards, which can be correctly interpreted and applied in clinical practice. We propose a set of recommendations for this purpose.

INTRODUCTION

Doppler velocimetry is used to assess small for gestational age fetuses (SGA) at risk for adverse perinatal outcome.¹ Doppler abnormalities in the umbilical artery are closely related to placental disease.² On the other hand, changes in the middle cerebral artery reflect fetal cardiovascular adaptations to hypoxia or blood flow redistribution.^{3, 4, 5} Thus, a decreased pulsatility index has been considered a compensatory phenomenon to protect the fetal brain in the context of fetal growth restriction (FGR).^{6,7,8,9} More recent work has suggested that the ratio of middle cerebral artery to umbilical artery PI – the cerebroplacental ratio (CPR) - is an independent predictor of fetal compromise¹⁰, caesarean section^{11,12} and adverse perinatal term outcomes^{13,14,15,16}. Therefore, umbilical, middle cerebral and CPR indices are currently used to modify the scheduling of antepartum surveillance and in some cases, to time delivery of the compromised fetus.^{2,10}

While the methodology for acquiring fetal Doppler signals has been standardized,¹⁷ multiple reference ranges have been reported. Patterns of Doppler progression have been clearly characterized.^{18,19,20,21,22} Thus, it has been reported that qualitative changes in UA Doppler, such as the presence, absence or reversal of end-diastolic velocity clearly increase the risk of fetal demise^{23,24,25} However, the association between pulsatility index (PI) quantitative changes in UA and MCA Doppler and the perinatal and long term outcomes has not been clearly established.^{26,27,28} Furthermore, the value of Doppler ultrasound in appropriately or large for gestational age, post-term pregnancies²⁹, diabetes³⁰ and uncomplicated dichorionic twin pregnancies³¹ remains uncertain³². We hypothesize that this lack of evidence may be at least partially explained by different Doppler references used to define normal or abnormal findings, as recently shown in a systematic review³³ of reference values for estimated fetal biometry.

The aim of this study was therefore to evaluate reference ranges for Doppler indices of UA, MCA, and CPR and specifically first, to assess the methodological quality of studies these are based on, using a set of predefined quality criteria for study design, statistical analysis and reporting methods; and second, to estimate the clinical impact of using different reference charts.

METHODS

This study was conducted and reported in accordance with the checklist proposed by the MOOSE group³⁴ and the PRISMA statement for reporting systematic reviews and meta-analyses.³⁵

Eligibility criteria, information sources and search strategy

A search strategy was formulated in collaboration with a professional information specialist (Appendix S1). Relevant studies were identified through a search of MEDLINE, EMBASE, CINAHL and the Web of Science databases including studies reported from 1954 through December 2016. Reference lists of retrieved full-text articles were examined for additional, relevant citations. The search was not restricted by study design or methodology, however only articles published in English or Spanish were considered.

Study selection

We included observational (cohort or cross-sectional) studies aimed to create reference ranges for Doppler indices of UA, MCA, and CPR. Studies were excluded if: (1) they were case-control studies; (2) their primary aim was not to construct Doppler reference ranges; and (3) studies limited to less than 20 weeks or more than 40 weeks (Appendix S1). All of the potentially relevant studies were retrieved and reviewed independently by two authors (SR-M and DO) to determine the inclusion. Disagreements were resolved through consensus (Appendix S3).

Methodological quality assessment

The methodological quality of the full-text versions of eligible studies was independently assessed by the same reviewers and a medical statistician (ES-U). Disagreements were resolved by consensus or consultation with two other reviewers

(ATP and EF). Authors' institutions were contacted in order to obtain a copy of the published article where this was not available from library sources.

A list of methodological quality criteria (Table 1) was initially developed by one of the authors of the present study (AC-A), modified for use in the setting of Doppler and agreed by the team not involved in data abstraction. These quality criteria are based on available published research,^{25,36,37} and are divided into three domains: study design, statistical methods, and reporting methods; in total, 24 quality criteria were evaluated.

Data extraction and synthesis

Following the review of included studies, all study details were entered into a Microsoft Excel 2010 spread sheet. Every study was assessed against each of the criteria within the checklist and were scored as either 0 or 1 if there was a 'high' or 'low' risk of bias, respectively. The overall quality score was defined as the sum of 'low risk of bias' marks (with the range of possible scores being 0–24). In order to assess agreement between reviewers in defining high or low risk of bias we calculated the Intraclass correlation coefficient (ICC) of the inter observer complete score; this suggested excellent agreement (0.815, 95% CI 0.66-0.90).

Multiple regression analysis was performed between quality scores and study characteristics which were not part of the scoring algorithm: year of publication, sample size of participating women, sample size of included ultrasound examinations, study duration, type of participating hospitals (teaching versus non-teaching), number of participating sites (single versus multi-site), and number of sonographers (single versus multiple). Statistical analyses were performed using Microsoft Excel 2010 and IBM SPSS Statistics version 20 (IBM, Armonk, NY).

RESULTS

The search yielded 2902 citations, of which 56 were considered for potential inclusion. The flow chart of the literature search is presented in Figure 1. Studies excluded from this review and the reasons for exclusion are listed in Appendix S2. A total of 38 studies from 22 countries met the inclusion criteria and were included in the final analysis. The main characteristics and overall, study design and statistical and reporting methods quality scores for each study included are presented in Table 2.^{38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75.}

The overall mean quality score for the included studies was 51.4% (95% Confidence interval (CI) 47.1 - 55.8), whereas quality scores for study design; and statistical and reporting methods were 47.4% (42.6 - 52.1) and 54.3% (48.8 - 59.7), respectively. The earliest study was published in 1988⁷⁵ and the latest in 2016.³⁸ The median sample size of participating women was 206 (range, 13-2323, interquartile range, 605), whereas the median number of ultrasound examinations was 513 (range, 60-2323; interquartile range, 742). In total, UA and MCA Doppler reference ranges were reported in 30 and 19 studies, respectively; in 11 studies reference ranges for both UA and MCA were reported, whereas only 4 studies reported reference ranges for CPR. The indices reported were the PI in 31 studies, the resistance index (RI) in 21 and the systolic-diastolic ratio (S/D) in 21 studies. The overall methodology score was similar for the studies focused on UA (median 49.0%; range 20.8-70.8), MCA (median 55.0%; range 29.1-79.1) and CPR (median 54.1%; range 41.6-62.5).

Data collection was prospective in 34 studies, but only in 19 studies was data collection explicitly for research purposes (Figure 2A; Table 2). Thirteen studies had a longitudinal design, 23 were cross-sectional, and one was mixed (cross-sectional and longitudinal); the design of the remaining study was not reported. Low-risk pregnancies were included in 22 (57.9%) studies. About half of the studies (52%) used a dating

method considered to be at low risk of bias, namely either first trimester measurement of crown rump length (CRL) alone or the maternal last menstrual period confirmed by CRL. Overall, the demographic characteristics of the populations and any inclusion or exclusion criteria were not described in detail.

The frequencies of 'low risk of bias' in each of the three groups of methodological criteria for the UA, MCA and CPR are presented in Figures 2-4. The highest risk of bias was similar for the UA, MCA and CPR, and was noted in the following fields: 'Multicentre study', where only three of the studies were performed in more than one center (Figures 2-4, item 1.10); 'Ultrasound quality control measures', where only two studies focused on the UA demonstrated a comprehensive quality assurance strategy, and where no study reported the use of an image scoring method for the purpose of ultrasound quality assurance (Figures 2-4, item 2.7); 'Sonographer experience', where only three and four studies of UA and MCA Doppler, respectively, clearly specified the experience or training of the sonographers (Figures 2-4, item 2.5); "Blinded measurements", where in only one UA study sonographers were blinded to the measurement recorded during the examination. (Figures 2-4, item 2.6); and 'Number of measurements', which was apparent in only three studies (Figures 2-4, item 2.9). Furthermore, none of the CPR studies reported information on "Recruitment period" (Figure 4, item 1.6).

Although some individual criteria of participant selection were used in different studies, there was no study in which all of these criteria were systematically used. (Figures 2-4, item 1.8). In the same line, sample size calculation was apparent in only seven studies (18,4%) (Figures 2-4, item 1.5).

Results from individual studies were reported in the form of tables, equations or charts as shown in Figures 2-4. Tables of mean and standard deviation (SD) of each

measurement and for each week of gestation were the most common methods of presentation (24 studies).

An equation for the mean and SD was reported in 23 of 38 studies, whereas printed charts of the median and percentile curves were seen in 25 publications.

With regard to type of hospital, teaching (N=28) did not have significantly higher overall quality scores as compared to non-teaching (N=10) hospitals (52.2% vs. 48.3%; $p=0.4$). In line with these results, but contrary to similar previous reports,²⁴ neither the year of publication ($p=0.506$) nor the sample size of participating women ($p=0.119$), ultrasound examinations ($p=0.215$), study duration ($p=0.251$), teaching hospital ($p=0.395$), number of participating sites ($p=0.278$) or sonographers ($p=0.447$) were significant predictors of quality score both on univariate or multiple regression analysis.

Differences in the studies that had the highest scores for quality UA, MCA and CPR showed that significant heterogeneity remained: for example, the 95th centile of UA PI at 37 weeks of gestation was 1.41 in one chart⁷¹, whereas the same cut-off value was 1.1 in another.⁴⁶ (Table 3) Standard situations were also noted at various other gestational ages and in reference ranges for MCA and CPR.

DISCUSSION

This study has shown considerable heterogeneity in the methodological quality used in ultrasound studies aimed at creating reference ranges for Doppler indices of UA, MCA, and CPR. These differences may at least partly explain the differences in reported reference ranges, and these in turn may explain some of the discrepancies seen in perinatal research based on Doppler including on patterns of Doppler progression^{76,19,20,21} or even long term outcomes.^{15,26} This review determined the potential risk of bias based on study design, statistical and reporting methods with a predefined quality-scoring sheet of 24 criteria to determine which of these studies are most likely to be relevant for clinical management.

Only in half of included studies the data were prospectively collected for research purposes. Therefore, using routinely collected clinical information to create a reference could be an important source of bias, with an over-representation of “at risk” cases. Therefore, 16 studies were performed in unselected populations, including pregnancies with suspected fetal growth restriction. Unselected population ensures a better representation of the underlying population.^{77,78} We consider that the aim of a fetal Doppler chart should be to depict how fetal hemodynamic should be under optimal conditions (a ‘prescriptive’ standard) rather than how they often grow (a ‘descriptive’ reference).⁷⁹

Three quarters of the published references were performed by one sonographer. Multi-sonographer studies increase external validity, and data consistency can be achieved by undertaking a formal standardization exercise prior to the start of a study.⁸⁰ A lack of blinding of researchers in studies has been shown to bias results⁸¹, and the STROBE guideline recommends blinding in order to reduce such bias⁸²; the effect of lack of blinding on expected value bias has also been demonstrated in the field of prenatal ultrasound, although the magnitude of the effect is not well understood. It is

suggested that such blinding should be undertaken in the research setting when creating ultrasound standards; but also in clinical practice in order to reduce such expected value bias^{83,84}; this occurred in only one study. Monitoring of ultrasound data quality through a comprehensive quality control strategy has been proposed as another way to ensure high quality, and should ideally include the use of image scoring methods and the assessment of intra- and interobserver variability of measurement.⁸⁵

Accurate estimation of gestational age is a fundamental prerequisite for creating any fetal standard.^{36,86,87} Only 20 studies used dating either by CRL alone, or by LMP corroborated by CRL.

Approximately one third of the studies did not report the results in the form of tables of fitted percentile values, gestational curve charts and regression equations for both the mean and standard deviation.⁸⁸ Both the median and variance should be modelled as a function of gestational age in a manner that accounts for the increasing variability with gestation and provides smooth percentile curves; goodness of fit testing should demonstrate that these curves describe accurately the structure of the raw data.⁴⁵

Even when assessing only those studies with the highest scores of methodological quality, clinical cut-offs varied significantly and could lead to important differences in clinical management, (Table 3) demonstrating that about 40-50% of fetuses may be misclassified by using one chart rather than another.

The main strength of this review lies in the rigorous methodology used, which included: (1) the implementation of guidelines for the conduct and reporting of systematic reviews of observational studies; (2) the inclusion of a relatively large number of studies in the review; and (3) the use of a quality score checklist used in previous studies^{13,36,37} which allowed an objective and quantitative assessment of study methodology. The use of a quality score in the form of a percentage allowed an

objective rather than empirical assessment of quality and also enabled regression analyses in order to identify predictors of quality or other trends.

A limitation of this study is the inclusion of studies published only in the English or the Spanish language. Therefore, it is possible that eligible studies published in other languages may have been missed. Finally, it may be possible that some biological variations might account for differences in Doppler results. For example, Doppler parameters obtained at very high altitudes^{89,90} may show some differences from measurements obtained near sea level due to adaptation; thus reference ranges from very high altitude may not be appropriate to be thought of as “normal” ranges, in the same way as study sites at high altitude sites were excluded when creating fetal growth standards⁹¹. In addition, most Doppler territories – but in particular those of the middle cerebral artery - show dynamic changes related to fetal movements, breathing or applied pressure from the US probe; however, while these changes can have an effect in an individual fetus, in studies creating ranges these should not lead to bias unless standard guidelines were not followed. Another potential limitation was that the reviewers who performed the data abstraction were not blinded to the origin and authors of the included studies.

This systematic review has identified many studies with poor methodology in ultrasound studies reporting reference ranges for Doppler indices of UA, MCA, and CPR. These should be taken into account in future studies and we recommend using a checklist of “methodological good practices” in further studies aimed at creating reference ranges for Doppler parameters of UA, MCA, and CPR; the criteria listed in under “low risk” of bias (Table 1) would constitute the optimal methodological aspects for any future study. Our aim was to recommend reference ranges for use in clinical services based on the lowest risk of methodological bias (Table 2), however, even among these studies there are differences of clinical importance in what is considered

normal and what is not; urgent research is needed to reach consensus on this issue or create charts of optimal quality for wide use.

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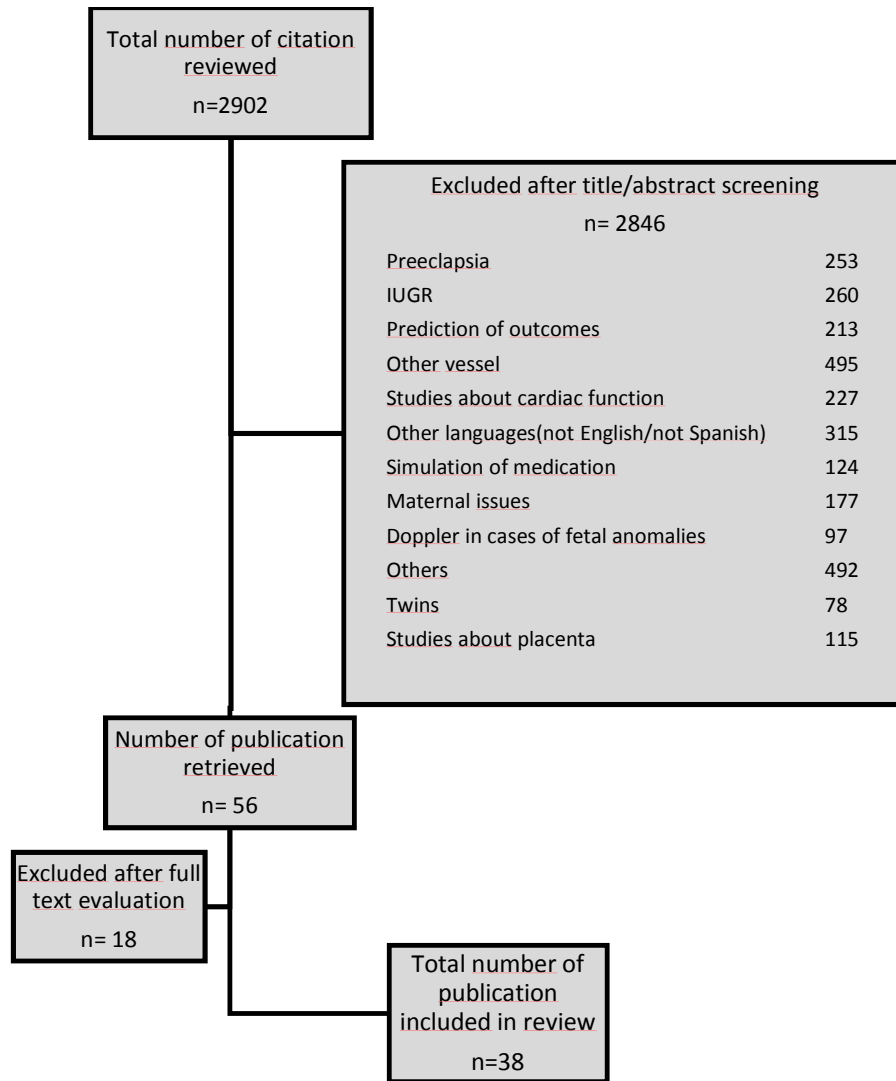
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Figure 1: Figure 1. Consort flow diagram of literature assessment.

Figure 2. Overall methodological quality of umbilical artery studies included in the review. (A) Study design (percentage of low risk of bias). (B) Reporting and statistical methods (percentage of low risk of bias).

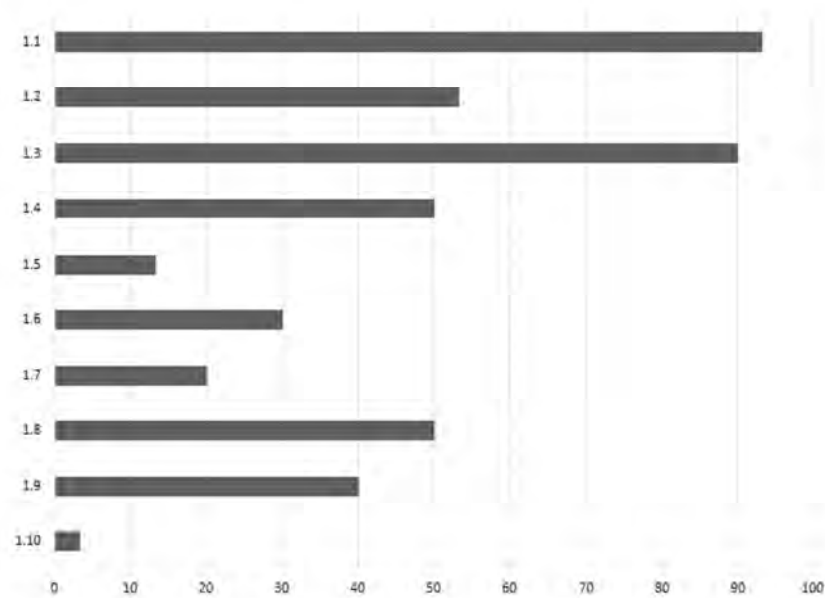
Figure 3. Overall methodological quality of middle cerebral artery studies included in the review. (A) Study design (percentage of low risk of bias). (B) Reporting and statistical methods (percentage of low risk of bias).

Figure 4. Overall methodological quality of cerebroplacental ratio studies included in the review. (A) Study design (percentage of low risk of bias). (B) Reporting and statistical methods (percentage of low risk of bias).



Figures Figure 2. Overall methodological quality of umbilical artery studies included in the review. (A) Study design (percentage of low risk of bias). (B) Reporting and statistical methods (percentage of low risk of bias).

A. Study design



B. Reporting and statistical

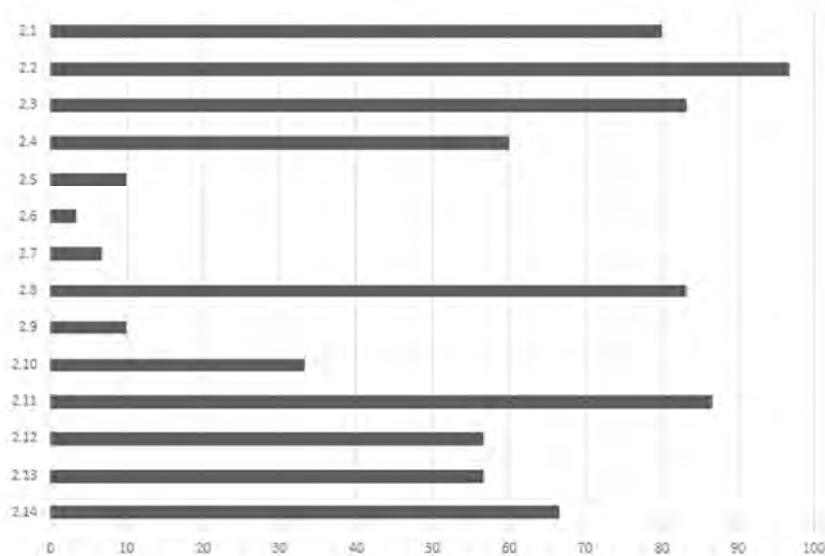
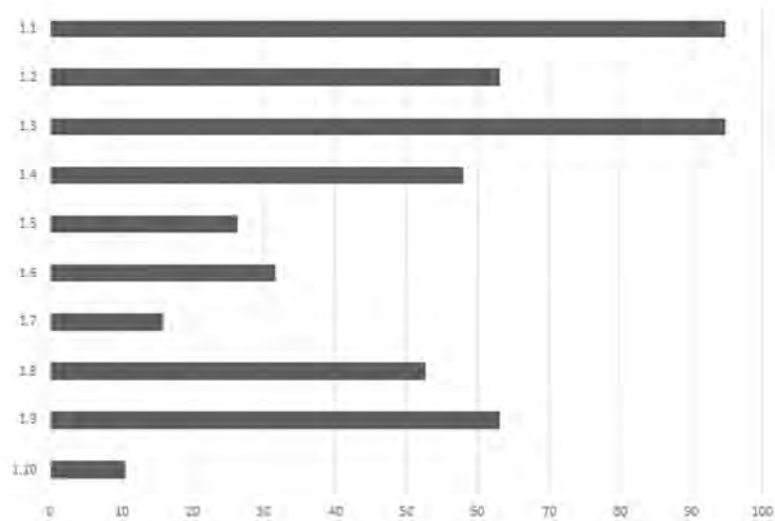


Figure 3. Overall methodological quality of middle cerebral artery studies included in the review. (A) Study design (percentage of low risk of bias). (B) Reporting and statistical methods (percentage of low risk of bias).

A. Study design



B. Reporting and statistical methods

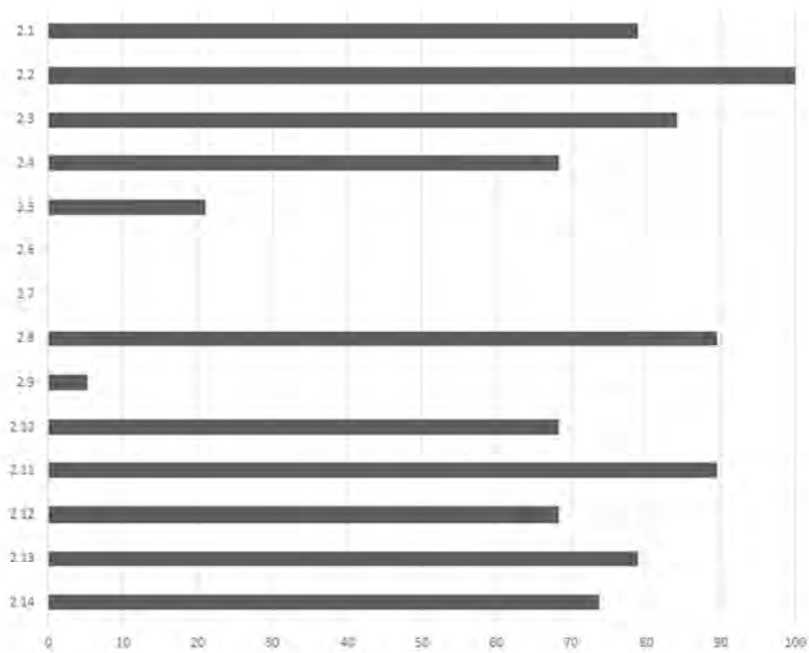
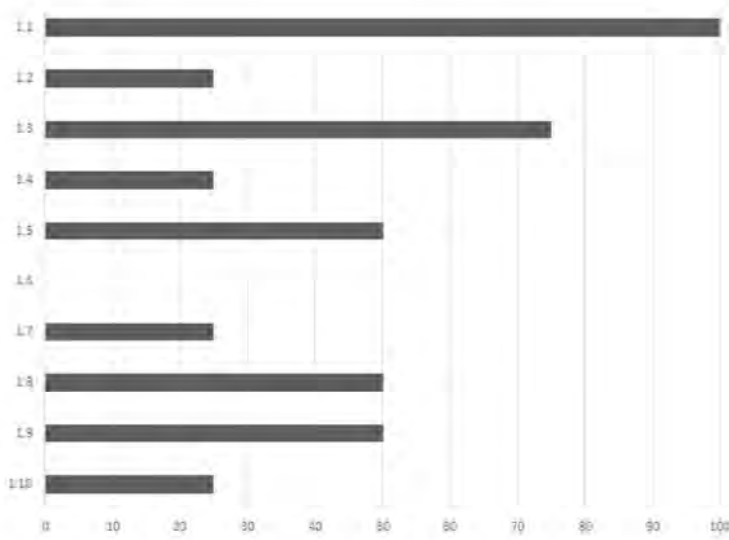


Figure 4. Overall methodological quality of cerebroplacental ratio studies included in the review. (A) Study design (percentage of low risk of bias). (B) Reporting and statistical methods (percentage of low risk of bias).

A. Study design



B. Reporting and statistical methods

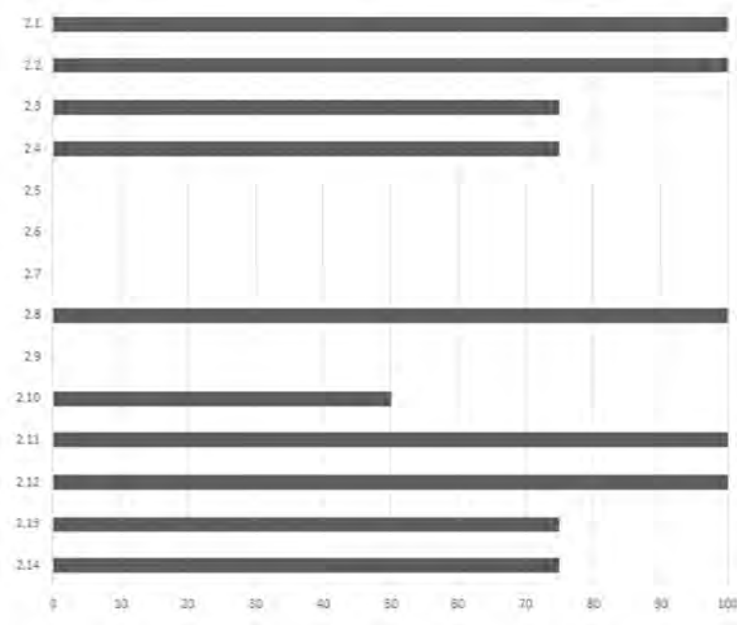


Table 1. Methodological quality criteria

Domain	Low risk of bias	High risk of bias
1.- STUDY DESIGN		
1.1 Design	Clearly described as either cross-sectional or longitudinal	Not reported Mixture of cross-sectional and longitudinal data
1.2 Population	Women were reported as coming from a population at low risk of pregnancy complications	Women come from an unselected population; or were selected: or at high risk of pregnancy complications; or not reported.
1.3 Prospective data collection	Prospective study and ultrasound data collected specifically for the purpose of constructing charts of fetal Doppler	Retrospective study, or data not collected specifically for the purpose of constructing charts of fetal Doppler, or unclear (e.g. use of routinely collected data)
1.4 Specific scan	Specific scan for research purposes	Routine scan in context of pregnancy assessment
1.5 Sample size	A priori determination or calculation of sample size and justification.	Lack of a priori sample size determination or calculation and justification
1.6 Recruitment period	Reported in months	Not reported
1.7 Consecutive enrolment	Consecutively included patients	Not consecutively included patients
1.8 Inclusion/exclusion criteria	<p>The study made it clear that women at high risk of pregnancy complications were not included, and that women with abnormal outcome were excluded, i.e. an effort was made to include 'normal' outcome as best possible.</p> <p>As a minimum, the study population should exclude:</p> <ul style="list-style-type: none"> – multiple pregnancy – fetuses with congenital structural or chromosomal anomalies – fetal death/stillbirth – women with disorders that may affect fetal growth or Doppler (at least should specify exclusion of women with pre-existing hypertension, diabetes mellitus, renal disease and smoking) – pregnancy complications (at least pre- 	<p>The study population included both low-risk and high-risk pregnancies, or women with abnormal outcome were not excluded.</p> <p>Study population that did not exclude fetuses or women with the characteristics previously described.</p> <p>Exclusions which would have a direct effect on the Doppler, such as fetuses found at birth to be small for dates.</p>

	eclampsia, SGA/IUGR, prematurity, diabetes mellitus, – deliveries prior 37 weeks	
1.9 Method of dating pregnancy	Clearly described Known last menstrual period (LMP) and a sonogram before 14 weeks demonstrating a crown–rump length (CRL) that corroborates LMP dates (within how many days unspecified)	Not described clearly Gestational age assessment at >14 weeks, or gestational age assessment not including ultrasonographic verification
1.10 Multicentre study	Study performed with more than one centre collaborating.	Only one hospital.
2.- REPORTING AND STATISTICAL METHODS	Low risk of bias	High risk of bias
2.1 Perinatal outcomes	Prospectively collected and reported	Not reported
2.2 Gestational age range	Reported	Not reported
2.3 Ultrasound machine(s) used and probe type	Clearly specified	Not clearly specified
2.4 Reported sonographers	Number of sonographers reported	Not clearly specified
2.5 Sonographers experience	Experienced or specifically trained sonographers clearly reported	Not clearly specified
2.6 Blinded measurements	Sonographers were blinded	Not clearly specified
2.7 Contains quality control measures	Should include the following: – assessment of intraobserver variability – assessment of interobserver variability – image review – image scoring – image storage	Does not contain quality control measures
2.8 Protocol	The study described sufficient and unambiguous details of the measurement techniques used for fetal Doppler parameters.	The study did not describe sufficient and unambiguous details of the measurement techniques used for fetal Doppler parameters
2.9 Number of measurements taken for	At least three measures per fetus per scan	Single measure or not specified

each Doppler variable		
2.10 Angle correction	Clearly specified	Not clearly specified
2.11 Statistical methods	Clearly described and identified	Not clearly described and identified
2.12 Report of mean and SD of each measurement and the sample size for each week of gestation	Presented in a table or clearly described	Not presented in a table or not clearly described
2.13 Report of regression equations for the mean (and SD if relevant) for each measurement)	Reported	Not reported
2.14 Scatter diagram	Study included Doppler Chart with mean and SD or centiles, at less 5 th centile, 50 th and 95 th centile.	Doppler Charts not included

Table 2. Included Studies – Quality scores for Study Design and reporting and statistical methods

STUDY	YEAR	COUNTRY	STUDY PERIOD (MONTHS)	WOMEN (N)	NUMBER OF SCAN	WEEKS	STUDY DESIGN	VESSELS	DOPPLER PARAMETERS	DATA COLLECTION	METHODS SCORE	DESIGN SCORE	TOTAL SCORE
Seffah et al ³⁸	2016	Ghana	5	470	458	20-40	Cross sectional	MCA	PI, RI, S/D RATIO	Prospective	78,57 (11/14)	70 (7/10)	75 (18/24)
Ayoola et al ³⁹	2016	Nigeria	12	400	400	15-39	Cross sectional	UA	PI, RI, S/D RATIO	Prospective	64,28 (9/14)	50 (5/10)	58,33 (14/24)
Morales-Rosello et al ⁴⁰	2014	Spain	NR	2323	2323	19-41	Cross sectional	MCA, CPR	PI	NR	50 (7/14)	30 (3/10)	41,66 (10/24)
Ferdousi et al ⁴¹	2013	Bangladesh	12	60	60	NR	Cross sectional	UA	PI, RI	NR	14,28 (2/14)	30 (3/10)	20,83 (5/24)
Bahlmann et al ⁴²	2012	Germany	NR	1926	1926	18-42	Cross sectional	UA	PI, RI	Prospective	57,14 (8/14)	40 (4/10)	50 (12/24)
Sutantawiboon et al ⁴³	2011	Thailand	12	658	658	13-40	Cross sectional	UA	PI, RI S/D RATIO	Prospective	35,71 (5/14)	40 (4/10)	37,50 (9/24)
Tarzamni et al ⁴⁴	2009	Iran	40	978	978	20-40	Cross sectional	MCA	PI, RI, S/D RATIO	Prospective	64,28 (9/14)	60 (6/10)	62,50 (15/24)
Tarzamni et al ⁴⁵	2008	Iran	40	978	978	20-40	Cross sectional	MCA	PI, RI, S/D RATIO	Prospective	71,42 (10/14)	60 (6/10)	66,66 (16/24)
Parra-cordero	2007	UK	18	172	172	23-41	Cross	UA, MCA	PI	Prospective	64,28	60	62,50

et al ⁴⁶							sectional				(9/14)	(6/10)	(15/24)
Ebbing et al ⁴⁷	2007	Norway	NR	161	566	19-41	Longitudinal	UA, MCA, CPR	PI	Prospective	64,28 (9/14)	60 (6/10)	62,50 (15/24)
Medina Castro et al ⁴⁸	2006	España/ Mexico	30	2081	2081	20-40	Cross sectional	UA	PI	Prospective	64,28 (9/14)	80 (8/10)	70,83 (7/24)
Medina Castro et al ⁴⁹	2006	España/ Mexico	31	727	727	20-40	Cross sectional	MCA	PI	Prospective	78,57 (11/14)	80 (8/10)	79,16 (19/24)
Konje et al ⁵⁰	2005	UK	NR	70	NR	24-38	Longitudinal	UA, MCA	PI, RI, S/D RATIO	Prospective	71,42 (10/14)	50 (5/10)	62,50 (15/24)
Acharya et al ⁵¹	2005	Norway	NR	130	513	19-42	Longitudinal	UA	PI, RI, S/D RATIO	Prospective	64,28 (9/14)	40 (4/10)	54,16 (13/24)
Komwilaisak et al ⁵²	2004	Thailand	6	312	312	20-37	Cross sectional	MCA	PI	Prospective	50 (7/14)	80 (8/10)	62,50 (15/24)
Ertan et al ⁵³	2003	NR	NR	370	602	28-40	Cross sectional	UA, MCA	PI, RI, S/D RATIO	Prospective	21,42 (3/14)	40 (4/10)	29,16 (7/24)
STUDY	YEAR	COUNTRY	STUDY PERIOD (MONTHS)	WOMEN (N)	NUMBER OF SCAN	WEEKS	STUDY DESING	VESSELS	DOPPLER PARAMETERS	DATA COLLECTION	METHODS SCORE	DESIGN SCORE	TOTAL SCORE
Baschat et al ⁵⁴	2003	Germany	NR	306	306	20-40	Cross sectional	UA, MCA, CPR	PI	Prospective	57,14 (8/14)	40 (4/10)	50 (12/24)
Bahlmann et	2002	Germany	NR	926	926	18-42	Cross	MCA	PI, RI	Prospective	78,57	50	66,66

al ⁵⁵							sectional					(11/14)	(5/10)	(16/24)
Meyberg et al⁵⁶	2000	Germany	NR	70	600	28-40	Longitudinal	MCA	RI, S/D RATIO	Prospective		21,42 (3/14)	40 (4/10)	29,16 (7/24)
Romero Gutierrez et al⁵⁷	1999	Mexico	NR	60	337	30-40	Longitudinal	UA	PI, RI	Prospective		42,85 (6/14)	60 (6/10)	50 (12/24)
Lakhkar et al⁵⁸	1999	India	12	71	NR	20-34	Longitudinal	UA	PI, RI, S/D RATIO	Prospective		28,57 (4/14)	40 (4/10)	33,33 (8/24)
Owen et al⁵⁹	1997	UK	NR	274	NR	26-41	Longitudinal	UA	PI, S/D RATIO	Prospective		42,85 (6/14)	50 (5/10)	45,83 (11/24)
Kurmanavicius et al⁶⁰	1997	Switzerland	NR	1675	1675	24-42	Cross sectional	UA, MCA, CPR	RI	Prospective		71,42 (10/14)	40 (4/10)	58,33 (14/24)
Manabe et al⁶¹	1995	Japan	NR	13	195	15-40	Longitudinal	UA, MCA	PI	Prospective		57,14 (8/14)	40 (4/10)	50 (12/24)
Rizzo et al⁶²	1994	Italy	NR	153	153	18-42	Cross sectional	UA, MCA	PI	Retrospective		35,71 (5/14)	40 (4/10)	37,50 (9/24)
Dilmen et al⁶³	1994	Turkey	11	550	550	16-41	Cross sectional	UA	PI, RI, S/D RATIO	Prospective		42,85 (6/14)	40 (4/10)	41,66 (10/24)
Rodriguez Ballesteros et al⁶⁴	1993	Mexico	12	123	335	20-40	Unclear	UA	S/D RATIO	Prospective		78,57 (11/14)	50 (5/10)	66,66 (16/24)
Duggan et al⁶⁵	1993	New Zeland	NR	19	NR	18-40	Longitudinal	UA	RI	Prospective		42,85	40	41,66

											(6/14)	(4/10)	(10/24)
Bruner et al⁶⁶	1993	USA	10	122	122	16-43	Cross sectional	UA	S/D RATIO	Unclear	64,28 (9/14)	30 (3/10)	50 (12/24)
Kofinas et al⁶⁷	1992	USA	NR	154	154	16-42	Cross sectional	UA	RI, S/D RATIO	Prospective	64,28 (9/14)	30 (3/10)	50 (12/24)
Pattinson et al⁶⁸	1989	South Africa	NR	45	NR	20-38	Longitudinal	UA	PI, RI, S/D RATIO	Prospective	50 (7/14)	50 (5/10)	50 (12/24)
Pearce et al⁶⁹	1988	UK	NR	34	NR	16-40	Longitudinal	UA	PI, RI, S/D RATIO	Prospective	57,14 (8/14)	40 (4/10)	50 (12/24)
Gerson et al⁷⁰	1987	USA	NR	171	NR	20-40	Cross sectional	UA	S/D RATIO	Prospective	50 (7/14)	50 (5/10)	50 (12/24)
STUDY	YEAR	COUNTRY	STUDY PERIOD (MONTHS)	WOMEN (N)	NUMBER OF SCAN	WEEKS	STUDY DESING	VESSELS	DOPPLER PARAMETERS	DATA COLLECTION	METHODS SCORE	DESIGN SCORE	TOTAL SCORE
Arduini et al⁷¹	1990	Italy	NR	1556	1556	20-42	Cross sectional	UA, MCA	PI	Prospective	57,14 (8/14)	60 (6/10)	58,33 (14/24)
Arstrom et al⁷²	1989	Sweeden	NR	22	NR	24-42	Longitudinal	UA, MCA	PI, RI, S/D RATIO	Prospective	57,14 (8/14)	40 (4/10)	50 (12/24)
Fogarty et al⁷³	1990	Ireland	NR	85	783	16-42	Longitudinal	UA	PI, RI, S/D RATIO	Prospective	57,14 (8/14)	50 (5/10)	54,16 (13/24)

Ferrazzi et al⁷⁴	1990	Italy	NR	482/150	NR	18-38	Cross sectional/ Longitudinal	UA, MCA	PI, S/D RATIO	Prospective	57,14 (8/14)	30 (3/10)	45,83 (11/24)
Wladimiroff et al⁷⁵	1988	Netherlands	NR	240	225	26-39	Cross sectional	UA	PI	Prospective	35,71 (5/14)	20 (2/10)	29,16 (7/24)

Table 3. Values of the 50th centile and for clinically relevant cut-offs (in brackets) for UA (95th centile), MCA (5th centile) and CPR (5th centile) from the highest scoring studies

Gestational age, weeks	Umbilical artery PI						Middle Cerebral Artery PI						Cerebroplacental ratio					
	Medina Castro et al		Parra-cordero et al		Arduini et al		Medina Castro et al		Seffah et al		Bahlman et al		Morales-Rosello		Ebbing		Baschat	
	50th centile	95th centile	50th centile	95th centile	50th centile	95th centile	50th centile	5th centile	50th centile	5th centile	Mean	5th centile	50th centile	5th centile	50th centile	5th centile	Mean	5th centile
28	1,06	1,41	1,07	1,45	1,12	1,61	1,77	1,17	1,96	1,03	1,94	1,44	1,73	1,23	2,14	1,47	2,13	1,28
29	1	1,46	1,04	1,4	1,08	1,57	1,89	1,12	1,92	0,91	1,94	1,44	1,76	1,25	2,21	1,53	1,86	1,15
30	1,03	1,39	1,01	1,36	1,05	1,54	1,92	1,18	1,75	1,42	1,92	1,42	1,79	1,25	2,28	1,58	2,34	1,44
31	1,03	1,37	0,98	1,32	1,02	1,51	1,93	1,14	1,77	1,51	1,9	1,40	1,81	1,26	2,32	1,62	2,29	1,73
32	1	1,35	0,95	1,28	0,99	1,48	1,82	1,15	1,54	1,41	1,88	1,37	1,82	1,26	2,35	1,64	2,03	1,24
33	0,96	1,3	0,92	1,24	0,97	1,46	1,8	1,11	1,66	1,11	1,74	1,33	1,82	1,25	2,36	1,65	2,1	1,44
34	0,97	1,29	0,89	1,2	0,95	1,44	1,7	1,12	1,52	1,29	1,8	1,28	1,81	1,24	2,35	1,63	2,1	1,36
35	0,93	1,27	0,86	1,17	0,94	1,43	1,63	1,07	1,32	1,08	1,75	1,23	1,79	1,22	2,32	1,6	2,01	1,45
36	0,92	1,21	0,84	1,13	0,92	1,42	1,6	0,99	1,38	1,03	1,68	1,16	1,77	1,2	2,27	1,55	2,01	1,26
37	0,86	1,18	81	1,1	0,92	1,41	1,45	0,85	1,53	1,01	1,61	1,09	1,73	1,17	2,19	1,48	2,25	1,17
38	84	1,12	79	1,06	0,91	1,4	1,37	0,79	1,14	0,96	1,53	1,01	1,69	1,14	2,09	1,4	1,9	1,23
39	0,83	1,05	0,76	1,03	0,91	1,4	1,24	0,75	1,37	0,77	1,45	0,92	1,64	1,1	1,97	1,29	1,64	1,16
40	0,79	1,07	0,74	1	0,91	1,4	1,06	0,56	0,99	0,92	1,35	0,82	1,58	1,06	-	-	1,8	1,08