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

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Short title: Reference ranges for fetal Doppler

Keywords: Doppler reference ranges, Small for Gestational Age, fetal growth restriction, umbilical artery Doppler, middle cerebral artery Doppler, Cerebroplacental ratio, methodology.

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.20102

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 growh resctriction (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 compromise[10], 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 pregnancies[29], diabetes[30] and uncomplicated dichorionic twin pregnancies[31] remains uncertain[32]. 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 review[33] 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 group[34] 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 references 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 1988[75] 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 chart[71], 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 results [81], and the STROBE guideline recommends blinding in order to reduce such bias[82]; 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 standards[91]. 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.

Acknowledgment

A. T. Papageorghiou is supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC).

REFERENCES

[1] Figueras F, Gardosi J. Intrauterine growth restriction: new concepts in antenatal surveillance, diagnosis, and management. Am J Obstet Gynecol. 2011 Apr;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. 2013 May;120(6):754-7. doi: 10.1111/1471-0528.12133. Epub 2013 Jan 15.
[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 Feb;32(2):103-12.
[4] Khalil A, Thilaganathan B. Role of uteroplacental and fetal Doppler in identifying fetal growth restriction at term. Best Pract Res Clin Obstet Gynaecol. 2017 Jan;38:38-47.
[5] Cruz-Martínez R, Figueras F, Hernandez-Andrade E, Oros D, Gratacos E. Fetal brain Doppler to predict cesarean delivery for nonreassuring fetal status in term small-for-gestational-age fetuses. Obstet Gynecol. 2011 Mar;117(3):618-26.
[6] Baschat AA, Viscardi RM, Hussey-Gardner B, Hashmi N, Harman C. Infant neurodevelopment following fetal growth restriction: relationship with antepartum surveillance parameters. Ultrasound Obstet Gynecol. 2009 Jan;33(1):44-50.
[7] Oros D, Figueras F, Cruz-Martinez R, Padilla N, Meler E, Hernandez-Andrade E, Gratacos E. Middle versus anterior cerebral artery Doppler for the prediction of perinatal outcome and neonatal neurobehavior in term small-for-gestational-age fetuses with normal umbilical artery Doppler. Ultrasound Obstet Gynecol. 2010 Apr;35(4):456-61.
[8] Baschat AA. Neurodevelopment following fetal growth restriction and its relationship with antepartum parameters of placental dysfunction. Ultrasound Obstet Gynecol. 2011 May;37(5):501-14.
[9] 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 Mar;44(2):249-56.
[10] Khalil , Morales-Rosello J, Morlando M, Hannan H, Bhide A, Papageorghiou A, Thilaganathan B. Is fetal cerebroplacental ratio an independent predictor of intrapartum fetal compromise and neonatal unit admission? Am J Obstet Gynecol. 2015 Jul;213(1):54.e1-10. doi: 10.1016/j.ajog.2014.10.024. Epub 2014 Oct 18.
[11] Cruz-Martínez R, Figueras F, Hernandez-Andrade E, Oros D, Gratacos E. Fetal brain Doppler to predict cesarean delivery for nonreassuring fetal status in term small-for-gestational-age fetuses. Obstet Gynecol. 2011 Mar;117(3):618-26.
[12] Garcia-Simon R, Figueras F, Savchev S, Fabre E, Gratacos E, Oros D. Cervical condition and fetal cerebral Doppler as determinants of adverse perinatal outcome after labor induction for late-onset small-for-gestational-age fetuses. Ultrasound Obstet Gynecol. 2015 Dec;46(6):713-7.
[13] Khalil AA, Morales-Rosello J, Elsaddig M, Khan N, Papageorghiou A, Bhide A, Thilaganathan B.The association between fetal Doppler and admission to neonatal unit at term. Am J Obstet Gynecol. 2015 Jul;213(1):57.e1-7. doi: 10.1016/j.ajog.2014.10.013. Epub 2014 Oct 15.
[14] Khalil A, Morales-Rosello J, Khan N, Nath M, Agarwal P, Bhide A, Papageorghiou A, Thilaganathan B Is cerebroplacental ratio a marker of impaired fetal growth velocity

and adverse pregnancy outcome? Am J Obstet Gynecol. 2017 Jun;216(6):606.e1-606.e10. doi: 10.1016/j.ajog.2017.02.005. Epub 2017 Feb 8

[15] DeVore GR. The importance of the cerebroplacental ratio in the evaluation of fetal well-being in SGA and AGA fetuses. Am J Obstet Gynecol. 2015 Jul;213(1):5-15.

[16] 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. (UOG19117). (In press)

[17] Bhide A, Acharya G, Bilardo CM, Brezinka C, Cafici D, Hernandez-Andrade E, Kalache K, Kingdom J, Kiserud T, Lee W, Lees C, Leung KY, Malinger G, Mari G, Prefumo F, Sepulveda W, Trudinger B. ISUOG practice guidelines: use of Doppler ultrasonography in obstetrics. Ultrasound Obstet Gynecol. 2013 Feb;41(2):233-39.

[18] Yoon BH, Romero R, Roh CR, Kim SH, Ager JW, Syn HC, Cotton D, Kim SW. Relationship between the fetal biophysical profile score, umbilical artery Doppler velocimetry, and fetal blood acid-base status determined by cordocentesis. Am J Obstet Gynecol. 1993 Dec;169(6):1586-94.

[19] Unterscheider J, Daly S, Geary MP, Kennelly MM, McAuliffe FM, O'Donoghue K, Hunter A, Morrison JJ, Burke G, Dicker P, Tully EC, Malone FD. Predictable progressive Doppler deterioration in IUGR: does it really exist?. Am J Obstet Gynecol. 2013 Dec;209(6):539.e1-7.

[20] Turan OM, Turan S, Gungor S, Berg C, Moyano D, Gembruch U, Nicolaides KH, Harman CR, Baschat AA. Progression of Doppler abnormalities in intrauterine growth restriction. Ultrasound Obstet Gynecol. 2008 Aug;32(2):160-7.

[21] Ferrazzi E, Bozzo M, Rigano S, Bellotti M, Morabito A, Pardi G, Battaglia FC, Galan HL. Temporal sequence of abnormal Doppler changes in the peripherals and central circulatory systems of the severely growth-restricted fetus. Ultrasound Obstet Gynecol. 2002;(19): p. 140-146.

[22] Oros D, Figueras F, Cruz-Martinez R, Meler E, Munmany M, Gratacos E. Longitudinal changes in uterine, umbilical and fetal cerebral Doppler indices in late-onset small-for-gestational age fetuses. Ultrasound Obstet Gynecol. 2011 Feb;37(2):191-5.

[23] Lees C, Marlow N, Arabin B, Bilardo CM, Brezinka C, Derks JB; TRUFFLE Group. Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). Ultrasound Obstet Gynecol. 2013 Oct;42(4):400-8.

[24] Thornton JG, Hornbuckle J, Vail A, Spiegelhalter DJ, Levene M; GRIT study group. Infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomised controlled trial. Lancet. 2004 Aug 7-13;364(9433):513-20.

[25] Caradeux J, Martinez-Portilla RJ, Basuki TR, Kiserud T, Figueras F. Risk of fetal death in growth-restricted fetuses with umbilical and/or ductus venosus absent or reversed end-diastolic velocities before 34 weeks of gestation: a systematic review and meta-analysis. Am J Obstet Gynecol. 2017 Dec 9. pii: S0002-9378(17)32331-1. doi: 10.1016/j.ajog.2017.11.566

[26] Morris RK, Say R, Robson SC, Kleijnen J, Khan KS. Systematic review and meta-analysis of middle cerebral artery Doppler to predict perinatal wellbeing. Eur J Obstet Gynecol Reprod Biol. 2012 Dec;165(2):141-55.

[27] Stampalija T, Arabin B, Wolf H, Bilardo CM, Lees C; TRUFFLE investigators. Is middle cerebral artery Doppler related to neonatal and 2-year infant outcome in early fetal growth restriction? Am J Obstet Gynecol. 2017 May;216(5):521.e1-521.e13. doi: 10.1016/j.ajog.2017.01.001. Epub 2017 Jan 10. Erratum in: Am J Obstet Gynecol. 2017 Sep;217(3):378.

[28] Alfirevic Z, Stampalija T, Medley N. Fetal and umbilical Doppler ultrasound in normal pregnancy. Cochrane Database Syst Rev. 2015 Apr 15;(4)

[29] D'Antonio F, Patel D, Chandrasekharan N, Thilaganathan B, Bhide A. Role of cerebroplacental ratio for fetal assessment in prolonged pregnancy. Ultrasound Obstet Gynecol. 2013 Aug;42(2):196-200. doi: 10.1002/uog.12357. Epub 2013 Jul 7.
[30] Graves CR. Antepartum fetal surveillance and timing of delivery in the pregnancy complicated by diabetes mellitus. Clin Obstet Gynecol. 2007 Dec;50(4):1007-13.
[31] Vayssière C, Benoist G, Blondel B, Deruelle P, Favre R, Gallot D, Jabert P, Lemery D, Picone O, Pons JC, Puech F, Quarello E, Salomon L, Schmitz T, Senat MV, Sentilhes L, Simon A, Stirneman J, Vendittelli F, Winer N, Ville Y; French College of Gynaecologists and Obstetricians.Twin pregnancies: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF). Eur J Obstet Gynecol Reprod Biol. 2011 May;156(1):12-7.
[32] American College of Obstetricians and Gynecologists. ACOG Practice bulletin no. 134: fetal growth restriction. Obstet Gynecol. 2013 May;121(5):1122-33.
[33] Ioannou C, Talbot K, Ohuma E, Sarris I, Villar J, Conde- Agudelo A, Papageorghiou AT. Systematic review of methodology used in ultrasound studies aimed at creating charts of fetal size. British Journal of Obstetrics and Gynaecology. 2012 Nov; 119(12): p. 1425-39.
[34] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. J Am Med Assoc 2000;283: 2008–12.
[35] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009 Jul 21;339:b2700.
[36] Napolitano R, Dhami J, Ohuma EO, Ioannou C, Conde-Agudelo A, Kennedy SH, Villar J, Papageorghiou AT. Pregnancy dating by fetal crown-rump length: a systematic review of charts.BJOG. 2014 Apr;121(5):556-65.
[37] Ohadike CO, Cheikh-Ismail L, Ohuma EO, Giuliani F, Bishop D, Kac G, Puglia F, Maia-Schlüssel M, Kennedy SH, Villar J, Hirst JE. Systematic Review of the Methodological Quality of Studies Aimed at Creating Gestational Weight Gain Charts. Adv Nutr. 2016 Mar 15;7(2):313-22. doi: 10.3945/an.115.010413. Print 2016 Mar.
[38]Seffah JD, Swarray-Deen A. Fetal middle cerebral artery Doppler indices and clinical application at Korle Bu Teaching Hospital, Accra, Ghana. Int J Gynaecol Obstet. 2016 Aug;134(2):135-9
[39] Ayoola OO, Bulus P, Loto OM, Idowu BM. Normogram of umbilical artery Doppler indices in singleton pregnancies in south-western Nigerian women. J Obstet Gynaecol Res. 2016 Dec;42(12):1694-1698
[40] 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 Feb;28(3):338-43
[41] Ferdousi MA, Sharif MM, Mohiuddin AS, Shegufta F. Normal value of pulsatility index of umbilical artery in second and third trimester of pregnancy. Bangladesh Med Res Counc Bull. 2013 Apr;39(1):42-4
[42] Bahlmann F, Fittschen M, Reinhard I, Wellek S, Puhl A. Blood flow velocity waveforms of the umbilical artery in a normal population: reference values from 18 weeks to 42 weeks of gestation. Ultraschall Med. 2012 Dec;33(7):E80-7
[43] Sutantawiboon A[1], Chawanpaiboon S. Doppler study of umbilical artery in Thai fetus. J Med Assoc Thai. 2011 Nov;94(11):1283-7.
[44] Tarzamni MK, Nezami N, Gatreh-Samani F, Vahedinia S, Tarzamni M. Doppler waveform indices of fetal middle cerebral artery in normal 20 to 40 weeks pregnancies. Arch Iran Med. 2009 Jan;12(1):29-34

[45] Tarzamni MK, Nezami N, Sobhani N, Eshraghi N, Tarzamni M, Talebi Nomograms of Iranian fetal middle cerebral artery Doppler waveforms and uniformity of their pattern with other populations' nomograms. BMC Pregnancy Childbirth. 2008 Nov 12;8:50.
[46] Parra-Cordero M, Lees C, Missfelder-Lobos H, Seed P, Harris C. Fetal arterial and venous Doppler pulsatility index and time averaged velocity ranges. Prenat Diagn. 2007 Dec;27(13):1251-7
[47] 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 Sep;30(3):287-96.
[48] Medina Castro N, Figueroa Diesel H, Guzmán Huerta M, Hernández Andrade E. [Normal reference values of the pulsatility index from the uterine and umbilical arteries during pregnancy] Ginecol Obstet Mex. 2006 Oct;74(10):509-15.
[49] Medina Castro N, Figueroa Diesel H, Hernández Andrade E[Normal reference values of the pulsatility index and peak systolic velocity in the fetal middle cerebral artery during normal pregnancy]. Ginecol Obstet Mex. 2006 Jul;74(7):376-82.
[50] Konje JC, Abrams KR, Taylor DJ. Normative values of Doppler velocimetry of five major fetal arteries as determined by color power angiography. Acta Obstet Gynecol Scand. 2005 Mar;84(3):230-7.
[51] Acharya G, Wilsgaard T, Berntsen GK, Maltau JM, Kiserud T. Reference ranges for serial measurements of umbilical artery Doppler indices in the second half of pregnancy. Am J Obstet Gynecol. 2005 Mar;192(3):937-44
[52] Komwilaisak R, Saksiriwuttho P, Ratanasiri T, Kleebkaow P, Seejorn K. Pulsatility index of the middle cerebral artery in normal fetuses. J Med Assoc Thai. 2004 Oct;87 Suppl 3:S34-7.
[53] Ertan AK, Hendrik HJ, Tanriverdi HA, Bechtold M, Schmidt W. Fetomaternal Doppler sonography nomograms. Clin Exp Obstet Gynecol. 2003;30(4):211-6.
[54] Baschat AA, Gembruch U. The cerebroplacental Doppler ratio revisited. Ultrasound Obstet Gynecol. 2003 Feb;21(2):124-7.
[55] Bahlmann F, Reinhard I, Krummenauer F, Neubert S, Macchiella D, Wellek S. Blood flow velocity waveforms of the fetal middle cerebral artery in a normal population: reference values from 18 weeks to 42 weeks of gestation. J Perinat Med. 2002;30(6):490-501
[56] Meyberg R, Ertan AK, Tossounidis I, Friedrich M, Schmidt W. Reference ranges and standard percentile-curves for the Doppler indices RI and S/D ratio of the fetal middle cerebral artery. Color Doppler measurements in a perinatal centre. Clin Exp Obstet Gynecol. 2000;27(2):106-8.
[57] Romero Gutiérrez G, Ponce de León AL, Ramos Palma S[Doppler flowmetric fetal indices in low-risk pregnancies]. Ginecol Obstet Mex. 1999 Oct;67:484-90.
[58] Lahkar BN, Ahamed SA. Doppler velocimetry of uterine and umbilical arteries during pregnancy. Indian J Radiol Imaging 1999;9:119-125
[59] Owen P, Ogston S. Standards for the quantification of serial changes in Doppler resistance indices from the umbilical arteriesEarly Hum Dev. 1997 Jul 24;49(1):39-47
[60] Kurmanavicius J[1], Florio I, Wisser J, Hebisch G, Zimmermann R, Müller R, Huch R, Huch A. Reference resistance indices of the umbilical, fetal middle cerebral and uterine arteries at 24-42 weeks of gestation. Ultrasound Obstet Gynecol. 1997 Aug;10(2):112-20.
[61] Manabe A, Hata T, Kitao M. Longitudinal Doppler ultrasonographic assessment of alterations in regional vascular resistance of arteries in normal and growth-retarded fetuses. Gynecol Obstet Invest. 1995;39(3):171-9.
[62] Rizzo G, Pietropolli A, Capponi A, Cacciatore C, Arduini D, Romanini C. Evaluation of pulsatility index nomograms based on fetal biometry in small for gestational age fetuses. J Ultrasound Med. 1994 Apr;13(4):267-74.

[63] Dilmen G, Aytaç S, Toppare MF, Oztürk M, Gökşin E. Umbilical artery blood flow characteristics in normal pregnancies. Gynecol Obstet Invest. 1994;38(2):96-9.
[64] Rodríguez Ballesteros R, López Sanchez ME, Chapa Fernandez JG, Galván Gonzalez JL, Olivares Morales AS. [Normal distribution curve for umbilical arterial flow velocimetry (S/D relation) measured by Doppler ultrasonography]. Ginecol Obstet Mex. 1993 Jun;61:171-5.
[65] Duggan P, McCowan L. Normal ranges for Doppler flow velocity waveforms from maternal uterine and fetal umbilical arteries. Aust N Z J Obstet Gynaecol. 1993 May;33(2):139-41.
[66] Bruner JP, Gabbe SG, Levy DW, Arger PH. Doppler ultrasonography of the umbilical cord in normal pregnancy. South Med J. 1993 Jan;86(1):52-5
[67] Kofinas AD, Espeland MA, Penry M, Swain M, Hatjis CG. Uteroplacental Doppler flow velocity waveform indices in normal pregnancy: a statistical exercise and the development of appropriate reference values. Am J Perinatol. 1992 Mar;9(2):94-101.
[68] Pattinson RC, Theron GB, Thompson ML, Lai Tung M. Doppler ultrasonography of the fetoplacental circulation--normal reference values. S Afr Med J. 1989 Dec 2;76(11):623-5.
[69] Pearce JM, Campbell S, Cohen-Overbeek T, Hackett G, Hernandez J, Royston JP. References ranges and sources of variation for indices of pulsed Doppler flow velocity waveforms from the uteroplacental and fetal circulationBr J Obstet Gynaecol. 1988 Mar;95(3):248-56.
[70] Gerson AG, Wallace DM, Stiller RJ, Paul D, Weiner S, Bolognese RJ. Doppler evaluation of umbilical venous and arterial blood flow in the second and third trimesters of normal pregnancy. Obstet Gynecol. 1987 Oct;70(4):622-6.
[71] Arduini D, Rizzo G. Normal values of Pulsatility Index from fetal vessels: a cross-sectional study on 1556 healthy fetuses. J Perinat Med. 1990;18(3):165-72
[72] Arström K, Eliasson A, Hareide JH, Marsal KFetal blood velocity waveforms in normal pregnancies. A longitudinal studyActa Obstet Gynecol Scand. 1989;68(2):171-8.
[73] Fogarty P, Beattie B, Harper A, Dornan J. Continuous wave Doppler flow velocity waveforms from the umbilical artery in normal pregnancy. J Perinat Med. 1990;18(1):51-7.
[74] Ferrazzi E, Gementi P, Bellotti M, Rodolfi M, Della Peruta S, Barbera A, Pardi G. Doppler velocimetry: critical analysis of umbilical, cerebral and aortic reference values. Eur J Obstet Gynecol Reprod Biol. 1991 Feb 25;38(3):189-96.
[75] Wladimiroff JW[1], Noordam MJ, van den Wijngaard JA, Hop WC. Fetal internal carotid and umbilical artery blood flow velocity waveforms as a measure of fetal well-being in intrauterine growth retardation. Pediatr Res. 1988 Nov;24(5):609-12.
[76] Baschat AA, Galan HL, Bhide A, Berg C, Kush ML, Oepkes D, Thilaganathan B, Gembruch U, Harman CR. Doppler and biophysical assessment in growth restricted fetuses: distribution of test results. Ultrasound Obstet Gynecol. 2006 Jan;27(1):41-7
[77] Altman DG, Chitty LS. Design and analysis of studies to derive charts of fetal size. Ultrasound Obstet Gynecol 1993;3:378–84.
[78] Rasmussen S. Charts to assess fetal wellbeing. Ultrasound Obstet Gynecol 2011;37:2–5.
[79] de Onis M, Garza C, Victora CG, Onyango AW, Frongillo EA, Martines J. The WHO Multicentre Growth Reference Study: planning, study design, and methodology. Food Nutr Bull 2004; 25:S15–26.
[80] Sarris I, Ioannou C, Dighe M, Mitidieri A, Oberto M, Qingqing W, Shah J, Sohoni S, Al Zidjali W, Hoch L, Altman DG, Papageorghiou AT; International Fetal and Newborn Growth Consortium for the 21st Century. Standardization of fetal ultrasound biometry measurements: improving the quality and consistency of measurements. Ultrasound Obstet Gynecol 2011;38:681–7.

[81] Hróbjartsson A, Thomsen AS, Emanuelsson F, Tendal B, Hilden J, Boutron I, Ravaud P, Brorson S. Observer bias in randomised clinical trials with binary outcomes: systematic review of trials with both blinded and non-blinded outcome assessors. BMJ 2012 Feb 27;344:e1119.
[82] Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. PLoS Med. 2007 Oct 16;4(10):e297.

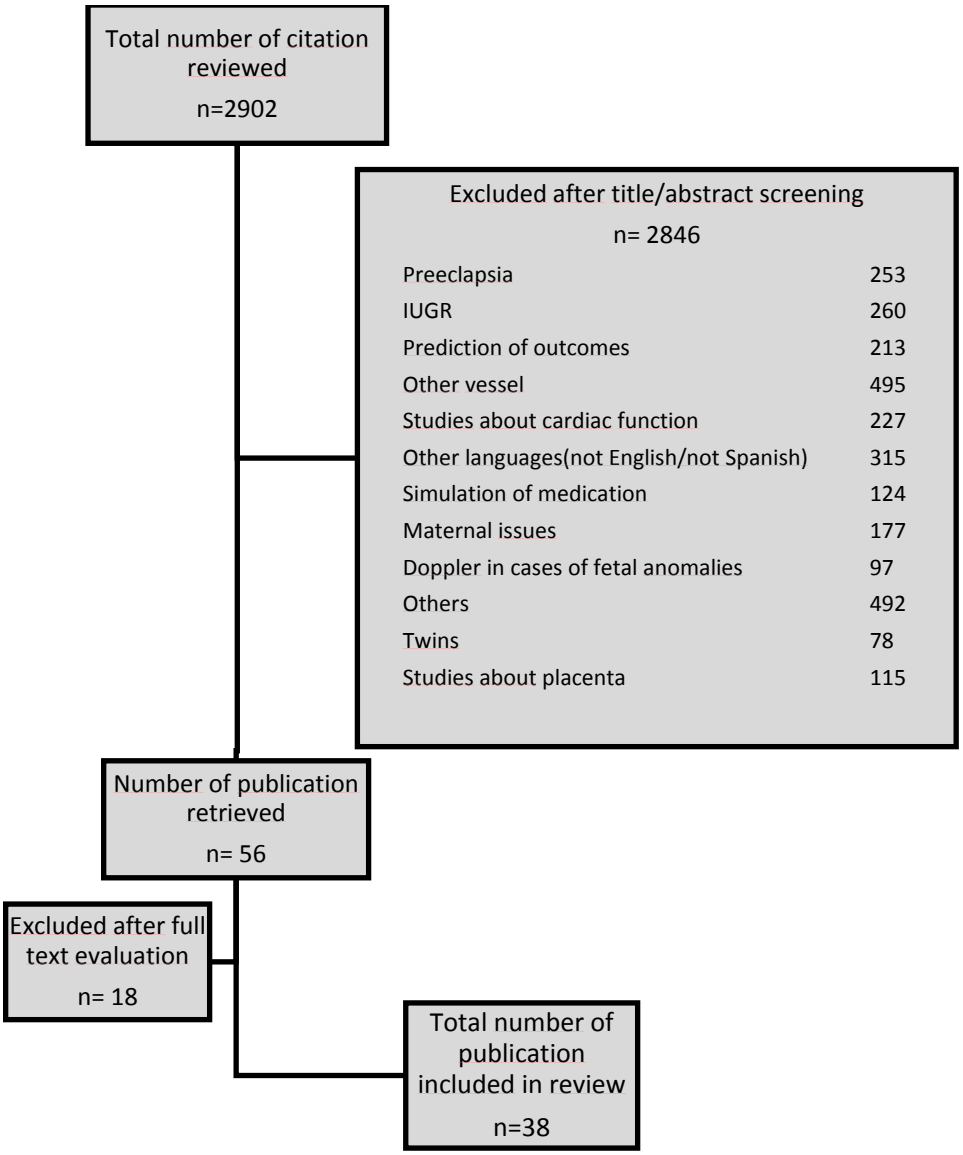
[83] Capmas P, Salomon LJ, Picone O, Fuchs F, Frydman R, Senat MV. Using Z-scores to compare biometry data obtained during prenatal ultrasound screening by midwives and physicians. Prenat Diagn. 2010 Jan;30(1):40-2.
[84] Salomon LJ, Bernard JP, Duyme M, Buvat I and Ville Y. The impact of choice of reference charts and equations on the assessment of fetal biometry. Ultrasound Obstet Gynecol 2005; 25: 559–565.
[85] Ruiz-Martinez S, Volpe G, S Vannuccini, A Cavallaro, LW Impey, AT Papageorghiou. An objective system to evaluate the quality of middle cerebral artery Doppler images. 27th World Congress of the International Society of Ultrasound in Obstetetrics and Gyneceolgy.
[86] Gardosi J. Dating of pregnancy: time to forget the last menstrual period. Ultrasound Obstet Gynecol 1997;9:367–8.
[87] Mongelli M, Wilcox M, Gardosi J. Estimating the date of confinement: ultrasonographic biometry versus certain menstrual dates. Am J Obstet Gynecol 1996;174:278–81.
[88] Altman DG, Chitty LS. Charts of fetal size: 1. Methodology. Br J Obstet Gynaecol 1994;101:29–34.
[89] Krampl E, Lees C, Bland JM, Espinoza Dorado J, Moscoso G, Campbell S. Fetal Doppler velocimetry at high altitude. Ultrasound Obstet Gynecol. 2001 Oct;18(4):329-34.
[90] Chen D, Zhou X, Zhu Y, Zhu T, Wang J. Comparison study on uterine and umbilical artery blood flow during pregnancy at high altitude and at low altitude. Zhonghua Fu Chan Ke Za Zhi. 2002 Feb;37(2):69-71.
[91] Papageorghiou AT, Ohuma EO, Altman DG, Todros T, Cheikh Ismail L, Lambert A, Jaffer YA, Bertino E, Gravett MG, Purwar M, Noble JA, Pang R, Victora CG, Barros FC, Carvalho M, Salomon LJ, Bhutta ZA, Kennedy SH, Villar J; International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. Lancet. 2014 Sep 6;384(9946):869-79.

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).

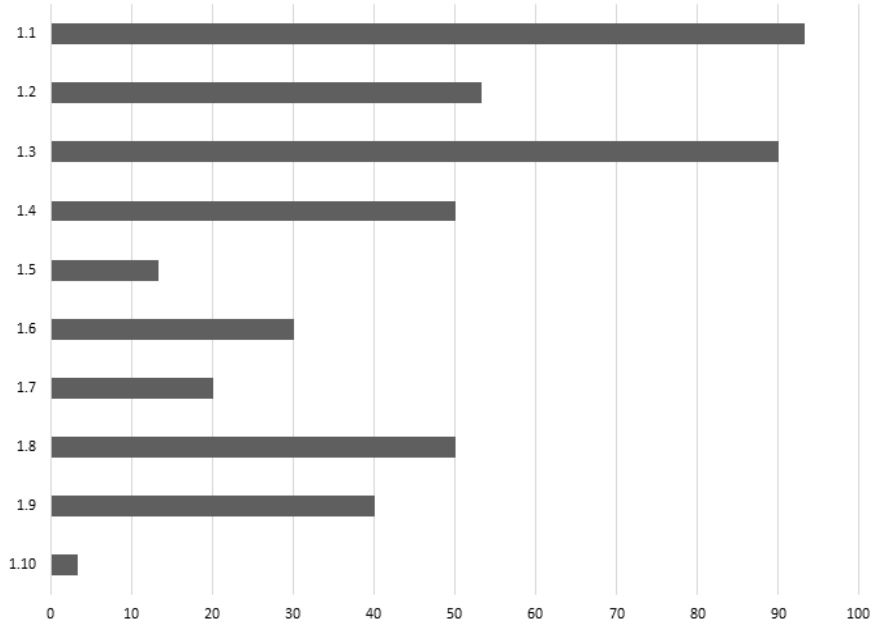
Figure 3. Overall methodological quality of middle cerebral artery studies included in the review. (A) Study design (percentage of low risk of bias). (B) Reporting and statistical methods (percentage of low risk of bias).

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).



FiguresFigure 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

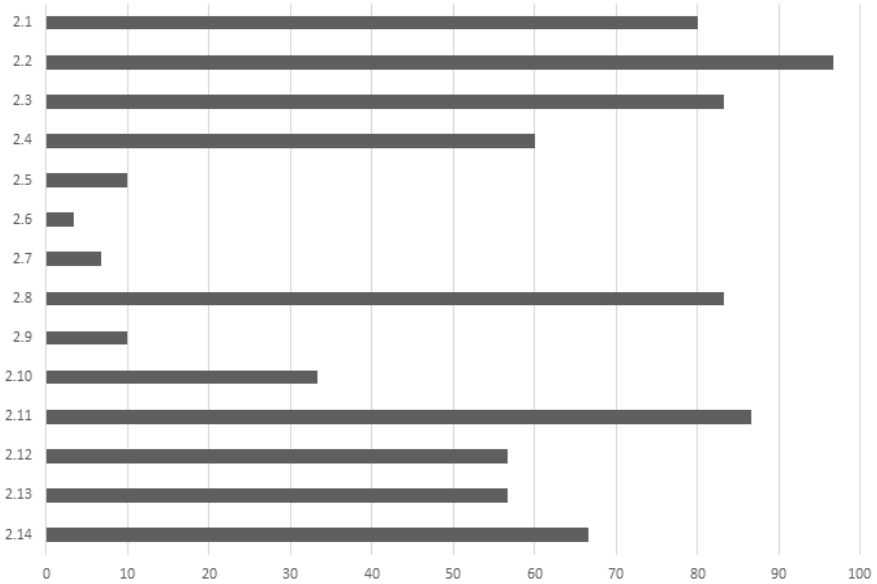
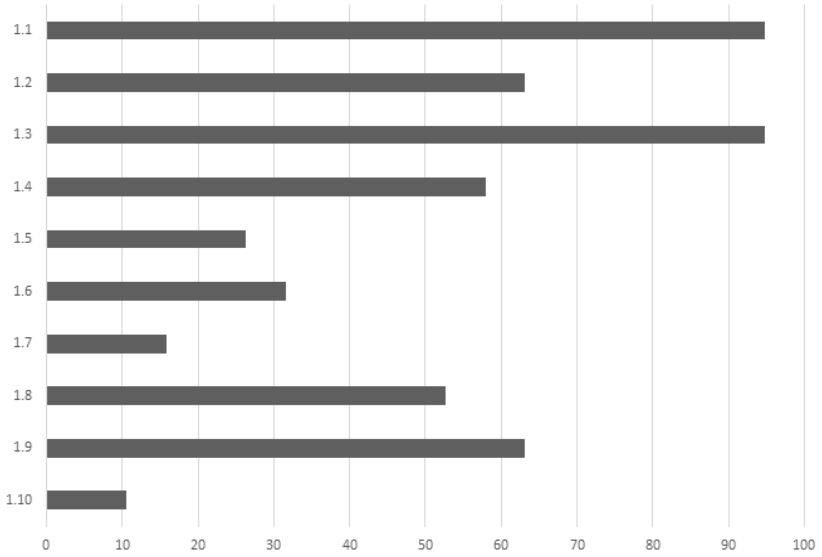


Figure 3. Overall methodological quality of middle cerebral artery studies included in the review. (A) Study design (percentage of low risk of bias). (B) Reporting and statistical methods (percentage of low risk of bias).

A. Study design



B. Reporting and statistical methods

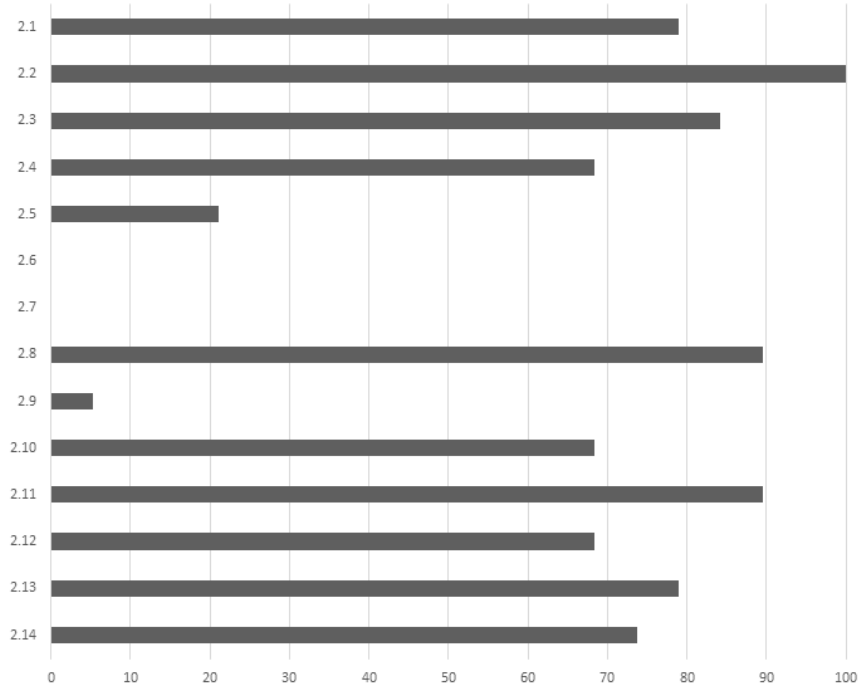
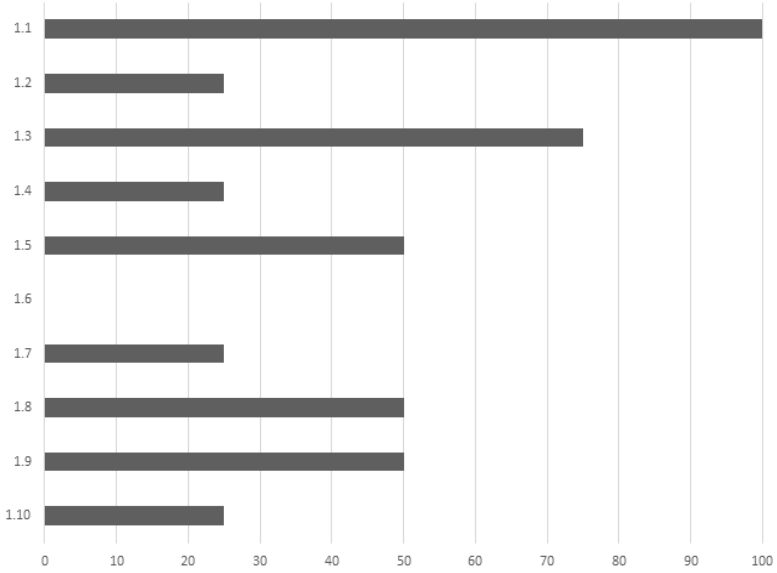


Figure 4. Overall methodological quality of cerebroplacental ratio studies included in the review. (A) Study design (percentage of low risk of bias). (B) Reporting and statistical methods (percentage of low risk of bias).

A. Study design



B. Reporting and statistical methods

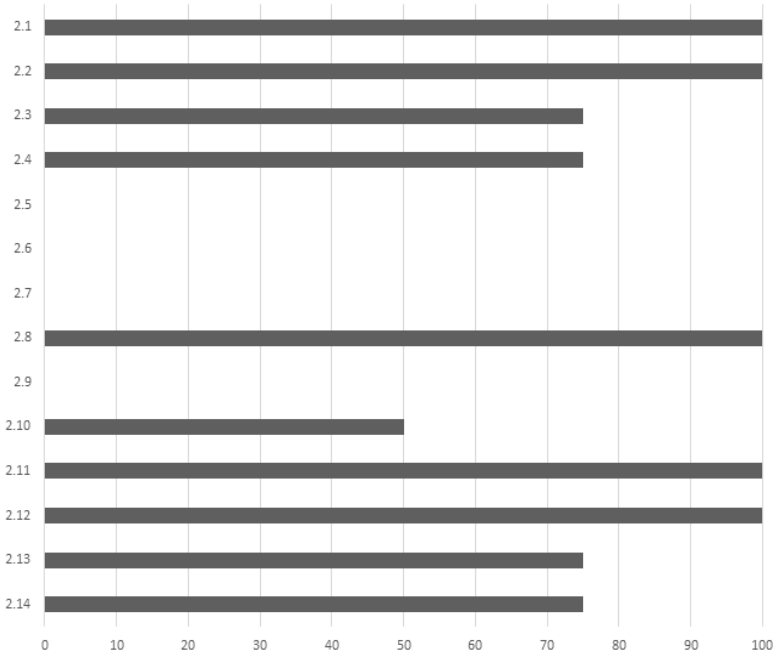


Table 1. Methodological quality criteria

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 hish 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	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. As a minimum, the study population should exclude: – 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-	The study population included both low-risk and high-risk pregnancies, or women with abnormal outcome were not excluded. Study population that did not exclude foetuses or women with the characteristics previously described. Exclusions which would have a direct effect on the Doppler, such as foetuses found at birth to be small for dates.

	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 DESING	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 al[56]	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 al[57]	1999	Mexico	NR	60	337	30-40	Longitudinal	UA	PI, RI	Prospective	42,85 (6/14)	60 (6/10)	50 (12/24)
Lakhkar et al[58]	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 al[59]	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 al[60]	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 al[61]	1995	Japan	NR	13	195	15-40	Longitudinal	UA, MCA	PI	Prospective	57,14 (8/14)	40 (4/10)	50 (12/24)
Rizzo et al[62]	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 al[63]	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 al[64]	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 al[65]	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 al[66]	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 al[67]	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 al[68]	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 al[69]	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 al[70]	1987	USA	NR	171	NR	20-40	Cross sectional	UA	S/D RATIO	Prospecrtive	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 al[71]	1990	Italy	NR	1556	1556	20-42	Cross seccional	UA, MCA	PI	Prospective	57,14 (8/14)	60 (6/10)	58,33 (14/24)
Arstrom et al[72]	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 al[73]	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 al[74]	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 al[75]	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