Clinical impact of Doppler reference charts to manage fetal growth restriction: need for standardization

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Abstract

Objective: To assess clinical variability in the management of fetal growth restriction according to published Doppler reference values for the umbilical artery (UA), middle cerebral artery (MCA) and cerebroplacental ratio (CPR).

Methods: We performed a systematic search of MEDLINE, EMBASE, CINAHL, and the Web of Science databases between the years 1954 and 2018, and selected studies with the sole aim of creating fetal Doppler reference values for the UA, MCA and CPR. Variations between clinically relevant pulsatility index (PI) cut-off values were assessed. Simulation analysis was performed on a cohort of small-for-gestational-age (SGA) fetuses (n=617) to evaluate the impact of this variability on clinical management.

Results: The 10 most cited articles for each index (UA-PI, MCA-PI and CPR) from a total of 40 studies that met the inclusion criteria were analyzed. Wide discrepancies in reported Doppler reference values were found. MCA-PI showed the greatest variability in clinically relevant cut-off values (MCA-PI<5^{th}) of up to 51% at term. However, the differences between the UA-PI (UA-PI>95^{th}) and CPR (CPR <5^{th} centile) cut-off values at each gestational age were from 20–40% and 15–35%, respectively. As expected by a simulation analysis, these differences showed great variability in the clinical management of SGA fetuses despite using the same protocol.

Conclusions: Selection of Doppler reference values can result in significant variability in the clinical management of intrauterine growth-restricted fetuses that may lead to suboptimal outcomes and inaccurate research conclusions. Therefore, an attempt to standardize fetal Doppler reference ranges is mandatory.

Introduction

Intrauterine growth restriction (IUGR) is a major cause of perinatal morbidity and mortality.[1] Apart from strict control during pregnancy and delivery, there are no other evidence-based treatments for suspected growth-restricted fetuses to ensure a healthy neonate that is not premature.[2,3] Currently, fetal ultrasound plays a critical role in the clinical management of IUGR.[4,5] The estimated fetal weight by ultrasound is the gold standard for the diagnosis of IUGR.[6] Nevertheless, Doppler measurement of foetal cardiovascular function is the basis for the schedule of controlled intervals and the optimum time to delivery.[7]

The methodology for the fetal Doppler evaluation is currently standardized.[8] Despite some controversy,[9] hemodynamic patterns of progression for early[10,11,12] and late[13] IUGR fetuses are well described. Qualitative changes in umbilical artery (UA) Doppler, such as absent or reverse diastolic flow, clearly indicate increased risk of fetal demise,[2,3,4,5] But the association between the sparing of the fetal brain, using UA, middle cerebral artery (MCA) pulsatility index (PI) Doppler, and cerebroplacental ration (CPR), and the perinatal and long-term outcomes has not been well determined.[14,15,16,17] Given the large number of published Doppler references, it could be hypothesised that this lack of evidence may be partially explained by the heterogeneity of this widespread use of different Doppler standards.

In a recent systematic review[18] we have shown that there is considerable methodological heterogeneity in studies reporting reference ranges for UA and MCA and CPR Doppler indices. The likely reason for these differences is due to methodological issues: thus, in the thirty-eight studies included, there was significant potential for bias – for example, only two studies reported on ultrasound quality control measures; there was unclear reporting of the experience and training of the sonographers; and lack of blinding of measurements in all but one study.

It was evident from that review that differences between reference charts would have important implications for clinical practice. In this study we wanted to quantify the effect of these differences in a clinical setting. In order to do this we aim to analyze the potential heterogeneity of the most frequently used published Doppler reference charts of the UA-PI, MCA-PI, and CPR and assess the influence of the variability on the clinical management of small-for-gestational-age (SGA) fetuses.

Methods

A systematic review was performed to identify studies that aimed to establish normal values for the UA-PI, MCA-PI and CPR. The search strategy was designed by a professional information specialist and included studies reported from 1954 through December 2018 in MEDLINE, EMBASE, CINAHL, and the Web of Science databases (Table S1). The search was not restricted by study design or methodology, but only articles published in English or Spanish solely aiming to establish normal values between 20 and 40 weeks of gestation were considered. The number of citations for each study was obtained from the Web of Knowledge.[19] This study was conducted and reported in accordance with the checklist proposed by the MOOSE group.[20]

Studies were retrieved and reviewed independently by two authors (SR and DO) to determine study inclusion. Disagreements were resolved through consensus with a third reviewer (ATP). We selected the 10 most cited studies for each vessel to compare the most used published Doppler reference standards. An UA-PI over the 95th percentile and MCA-PI and CPR below the 5th percentile were considered to be clinically relevant cut-off values.[4,5,7] Clinical cut-off percentiles were calculated by the mean and standard deviation for gestational age when not reported by the authors.[21,22] Variability was expressed as a percentage and was obtained by subtracting the lowest PI value from the highest and dividing by the highest PI value for every week of gestation.

Finally, simulation analysis was performed on a cohort of 617 consecutive fetuses with an estimated fetal weight (EFW) below the 10th percentile[23], assessed in our centre from 24–41 weeks of gestation. IUGR was defined as an EFW below the 10th percentile accompanied with whichever abnormal Doppler (UA-PI>95th, MCA-PI<5th, or CPR<5th); in which labour induction was recommended at 37 weeks of gestation.[4,5,7]

To assess the influence of the Doppler reference standard variability in the clinical management of SGA fetuses, every case was hypothetically classified and theoretically managed according to the same previously described protocol, using the highest and lowest cut-off values for the UA-PI, MCA-PI, and CPR for every gestational age.

Statistical analyses were performed using Microsoft Excel 2010 and IBM SPSS Statistics version 20.

Results

The database searches yielded 6243 possible citations for our systematic review. Figure 1 shows the entire process of analysis and selection of the studies. Forty published papers met the selection criteria, with their sole objective being to determine reference Doppler values. In accordance with our objective to determine the clinical impact of variability, we selected the Doppler reference values most used in clinical practice and research. Thus, we included the top 10 most cited Doppler reference values for MCA-PI and CPR. We included 13 UA-PI Doppler reference values instead of 10 to avoid selection bias, because four articles focused on UA presented the same number of citations. We only found five articles showing reference ranges of CPR. Table 1 describes the main characteristics and number of citations of the 19 selected studies.

The distribution of UA-PIs within the 95th percentile across all pregnancies for each study is plotted in Figure 2. Similarly, MCA-PIs and CPR within the 5th percentiles were plotted and are shown in Figures 3 and 4. Notably, great variability existed between the reference values for the different UA-PI, MCA-PI and CPR cut-offs, with clinical implications. Furthermore, many of the most cited references in the literature showed an anomalous distribution of their PI cut-off values during gestation, possibly due to inappropriate statistical analyzes[18].

Differences between the highest and lowest published values for each week of gestation for the UA-PI within the 95th percentile and MCA-PI and CPR within the 5th percentiles are expressed as percentages and are shown in Figure 5. The mean between the difference of the highest and lowest UA-PI within the 95th percentile for each complete gestational age was 28.02% (range: 21–41%). These differences were much more marked in the case of the highest and lowest cut-off values for each gestational week for the MCA-PI within the 5th percentile, with a mean difference of 36.86% (range: 26.8–51.3%). These differences increased after 35 weeks of gestation, where the presence of an abnormal MCA-PI involves important modifications for clinical management. Finally, CPR presented the lowest variability, with a mean difference of 24.09% (range: 15–32.6%). Again, as expected, the highest variability for CPR was at term.

To evaluate the potential impact of this variability among Doppler PI cut-offs on clinical management, simulation analysis of a historical cohort of 617 consecutive SGA fetuses was performed (Table 2). Depending on the choice of the lowest or highest UA-PI greater than the 95th percentile and MCA-PI and CPR less than the 5th percentiles for each gestational age, the proportions of SGA fetuses classified as abnormal according to UA-PI, MCA-PI, and CPR varied from 24.5–2.1%, 0.9–23.1%, and 5.5–33.1%, respectively. According to several clinical guidelines,[4,5] induction of labour may be required for UA-PI$>95^{th}$ percentile, MCA-PI$<5^{th}$, or CPR$<5^{th}$ percentiles at full term. Even following the same clinical protocol, the potential number of labour inductions for SGA fetuses at term could vary from 33.7–2.1%, 1.1–13.3%, and 5.6–23.3% depending on the PI cut-off variability of the UA, MCA, and CPR, respectively.

Discussion

This is the first systematic review to analyze the impact of variability among the most used Doppler reference charts on the clinical management of SGA fetuses.

In most cases, fetal growth restriction is thought to be a marker of uteroplacental insufficiency.[24] Angiogenic defects that result in placental pathology are collectively referred to as maternal vascular lesions of underperfusion.[25] Hence, UA-PI can indirectly reflect the dimensions of the villous vascular tree, blood flow resistance in the fetal compartment of the placenta, and relative risk of nutritional and metabolic deficiency[26,27]. Besides, a growing body of evidence suggests that MCA Doppler, alone or in combination with the UA-PI (i.e., CPR), may be helpful in identifying fetuses at risk of IUGR[28,29,30] as a surrogate marker of the redistribution of blood flow for vital organ prioritization[15]. UA-PI, MCA-PI and CPR are now the most widely used tool for control and decision making for SGA fetuses[4,5]. UA-PI vasoconstriction is defined according to a statistical cut-off of the 95th percentile[31]. Similarly, the 5th percentile defines brain vasodilation for the MCA-PI or CPR[31]. Therefore, appropriate Doppler reference values are needed to accurately estimate these cut-off points. Unfortunately, a systematic review recently published by our group revealed considerable methodological heterogeneity in studies reporting reference ranges for UA-PI, MCA-PI and CPR[18]. In this study, we showed large differences among fetal Doppler reference charts at clinically relevant cut-off values.

For our analysis, we rationed the most cited studies in the literature to be the most used for clinical practice and research purposes. The application of an appropriate methodology in these studies to fit the criteria for our study has been previously described [18,32]. However, all the works included in this analysis present a high risk of bias in their design and methodology and no good correlation exists between the methodological quality and number of citations in the literature[18]. For example, the top three most cited studies by Arduni[34], Baschat[35], and Acharya[36] showed an important risk of bias due to the fact that they were only the sixth, eleventh, and ninth ranked studies based on methodological quality according to a recently published systematic review[18]. It could be argued that older works are more likely to be cited than more recent studies with higher quality methodology[33] because newer works have not had sufficient time to implant themselves in clinical practice.

We found important sources of bias in the most widely used studies.[18] Ultrasounds were not performed for research purposes,[34,35,38,40,43,44,50] neither the recruitment period,[34,35,37,38,39,41,42,44,48] or perinatal results were described,[34] and the study was performed at a single centre.[34,35,36,37,38,39,40,41,47,49] We also found a lack of reporting necessary sample sizes,[34,36,38,39,40,41,44,45,46,48,50] the gestational dating method,[35,36,37,38,41,50] experience of the sonographers,[34,36,37,38,41,43,44,49,50] and even the inclusion and exclusion criteria[36,38,39,41,44,49] and quality controls.[34,35,36,37,38,39,40,41,43,44,45,46,47,48,49,50] As shown in Figures 2, 3, and 4, an irregular distribution was observed among the cut-off values at gestational time points in many of the analyzed reference ranges, suggesting inappropriate statistical treatment of the data.

Identification of fetal risk of adverse outcomes is a challenge in perinatal medicine. The main objective for strict control of IUGR fetuses is to deliver a healthy newborn without extreme prematurity, but also in avoidance of intrauterine death and maternal or neonatal morbidity. We want to highlight the impact of the heterogeneity of the Doppler reference values being used within clinical practice and research. Simulation analysis performed in a real cohort of SGA fetuses clearly showed that the use of inaccurate tools can lead to inaccurate decision making for important clinical issues. The optimal time for pregnancy completion for SGA fetuses is one of the main focuses of interest in IUGR research.[53,54,55] , according to our results, even with the use of a standardized clinical protocol, the Doppler reference values used have a significant clinical impact. For example, a rate of induction at term could range from 2.1–33.7% for UA-PI, 1.1–13.3% for MCA-PI, and 5.6–22.3% in the case of CPR. Notably, the broadest variation among the Doppler reference values is at full term, which is a critical moment to programme different therapeutic actions. From our point of view, this potential variability in the clinical management of SGA fetuses is unacceptable.

The main strength of this study lies in the rigorous methodology used; we performed a comprehensive systematic review including a relatively large number of studies. A limitation of this study is that the evaluation of the impact of Doppler reference value charts in clinical management was performed in a retrospective cohort of SGA fetuses controlled with specific Doppler references. Thus, our results could be potentially biased. Due to the high number of published Doppler value reference charts, it is unlikely that a prospective study with a similar aim was conducted. Another potential limitation of this study is the inclusion of studies published only in the English or Spanish language. Nevertheless, this restriction is unlikely to be a significant limitation because the top-cited Doppler reference value charts were always published in English, as expected. Additionally, the literature search did not have restrictions for year of publication because some of the older ultrasound Doppler studies are still used in current clinical practice. Apart from the PI, other parameters such as systolic/diastolic ratio (S/D) are sometimes used for the management SGA fetuses. We did not include this analysis for two reasons: firstly, only three of the most cited published Doppler references (Ayoola[50], Acharya[36] and Fogarty[42]) give reference ranges for the umbilical artery S/D ratio, and one (Tarzamni[43]) mention the middle cerebral artery S/D ratio. Secondly, as we did not have data on the S/D ratio from the cohort of SGA fetuses that we used to perform the simulation analysis, this could not be included here. Although this is a potential limitation the relationship between PI, RI, S/D ratios mean that the principle, of reaching different clinical decisions depending on the reference chart used, still applies.

The selection of the Doppler reference values determines the significant variability in the clinical management of IUGR fetuses that may lead to suboptimal outcomes and inaccurate research conclusions. In conclusion, an attempt to standardize fetal Doppler reference ranges is mandatory.

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BIBLIOGRAPHY

[1] Sharma D, Shastri S, Sharma P. Intrauterine Growth Restriction: Antenatal and Postnatal Aspects. Clin Med Insights Pediatr. 2016 Jul 14;10:67-83.

[2] 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.

[3] 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.

[4] Royal College of Obstetricians and Gynecologists. Small-for-Gestational-Age Fetus, Investigation and Management (Green-top Guideline No. 31) RCOG Green-top Guideline, 2nd Edition;2014 (cited 2016 Dec 6th) Available from: https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_31.pdf.

[5] American College of Obstetricians and Gynecologists. ACOG Practice bulletin no. 134: fetal growth restriction. Obstet Gynecol. 2013 May;121(5):1122-33.

[6] Stirnemann J, Villar J, Salomon LJ, Ohuma E, Ruyan P, Altman DG, Nosten F, Craik R, Munim S, Cheikh Ismail L, Barros FC, Lambert A, Norris S, Carvalho M, Jaffer YA, Noble JA, Bertino E, Gravett MG, Purwar M, Victora C, Uauy R, Bhutta Z, Kennedy S, Papageorghiou AT; for the International Fetal Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st).International Estimated Fetal Weight Standards of the INTERGROWTH-21st Project. Ultrasound Obstet Gynecol. 2016 Nov 2. [Epub ahead of print]

[7] 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.

[8] 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.

[9] 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.

[10] 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.

[11] 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.

[12] Ferrazzi E, Bozzo M, Rigano S, Bellotti M, Morabito A, Pardi G, Battaglia FC, Galab 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.

[13] 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.
[14] 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.
[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] Alfirevic Z, Stampalija T, Medley N.Fetal and umbilical Doppler ultrasound in normal pregnancy. Cochrane Database Syst Rev. 2015 Apr 15;(4)
[17] 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.
[18] Oros D, Ruiz-Martinez S, Staines-Urias E, Conde-Agudelo A, Villar J, Fabre E, Papageorghiou AT. Reference ranges for Doppler indices of umbilical and middle cerebral arteries and cerebroplacental ratio: a systematic review. Ultrasound Obstet Gynecol. 2018 Aug 20. doi: 10.1002/uog.20102.
[19] Clarivate Analytics 2019. Web of Science. Avaible from: https://apps.webofknowledge.com
[20] 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.
[21] De Vore GR, Cuneo BF, Satou GM, Sklansky M. How to determne the percent of study subjects below the 5th or above the 95th centiles of the control group when only the mean and standard deviation are provided. Ultrasound Obstet Gynecol. Doi: 10.1002/uoog.20110
[22] Royston P, Wright EM. How to construct 'normal ranges' for fetal variables. Ultrasound Obstet Gynecol 1998;11:30–8.
[23] Figueras F, Meler E, Iraola A, Eixarch E, Coll O, Figueras J, Francis A, Gratacos E, Gardosi J. Customized birthweight standards for a Spanish population. Eur J Obstet Gynecol Reprod Biol. 2008 Jan;136(1):20-4.
[24] Labarrere CA, DiCarlo HL, Bammerlin E, Hardin JW, Kim YM, Chaemsaithong P, Haas DM, Kassab GS, Romero R. Failure of physiologic transformation of spiral arteries, endothelial and trophoblast cell activation, and acute atherosis in the basal plate of the placenta. Am J Obstet Gynecol. 2017 Mar;216(3):287.e1-287.e16.
[25] Parra-Saavedra M, Crovetto F, Triunfo S, Savchev S, Peguero A, Nadal A, Parra G, Gratacos E, Figueras F. Placental findings in late-onset SGA births without Doppler signs of placental insufficiency. Placenta. 2013 Dec;34(12):1136-41.
[26] 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
[27] 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.
[28] Smith A, Flatley C, Kumar S. The risk of preterm birth associated with a low cerebroplacental ratio. J Matern Fetal Neonatal Med. 2019 Feb;32(4):610-616. doi: 10.1080/14767058.2017.1387889. Epub 2018 Feb 15.
[29] 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.
[30] Vollgraff Heidweiller-Schreurs CA, De Boer MA, Heymans MW, Schoonmade LJ, Bossuyt PMM, Mol BWJ, De Groot CJM, Bax CJ. Prognostic accuracy of cerebroplacental ratio and middle cerebral artery Doppler for adverse perinatal outcome: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018 Mar;51(3):313-322. doi: 10.1002/uog.18809. Epub 2018 Feb 5.
[31] Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, Silver RM, Wynia K, Ganzevoort W. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol. 2016 Sep;48(3):333-9. doi: 10.1002/uog.15884.
[32] Mccarthy E, Walker S, Shub A. Umbilical artery Doppler flow: An examination of current and best practice. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2013; 53: p. 403-407.
[33] 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
[34] 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): p. 165-72
[35] Baschat A, Gembruch U. The cerebroplacental Doppler ratio revisited. Ultrasound Obstet Gynecol. 2003 Feb; 21(2): p. 124-7.
[36] 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
[37] 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): p. 287-96.
[38] Wladimiroff J, Noordam M, van der Wijngaard J, Hop W. Fetal internal carotid and umbilical artery blodd flow velocity waveforms as a measure of fetal well.being in intrauterine growth retardation. Pediatr Res. 1988 Nov; 24(5): p. 609-12.
[39] 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. 30 (2002) 490–501
[40] Parra-Cordero M, Lees C, Missfelder-Lobos H, Seed P, Harris C. Fetal arterial and venous Doppler pulsatility index and time averaged velocity ranges. Prenatal Diagn. 2007 Dec; 27(13): p. 1251-7.

[41] Manabe A, Hata T, Kitao M. Longitudinal Doppler ultrasonographic assesment of alterations in regional vascular resistance of arteries in normal and growth-retarded fetuses. Gynecol Obstet Invest. 1995; 39(3): p. 171-9.
[42] Fogarty P, Beattie B, Harper A, Dornan J. Continuos wave Doppler flow velocity waveforms from the umbilical artery in normal pregnancy. J Perinat Med. 1990; 18(1): p. 51-7.
[43] Tarzamni M, 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): p. 29-34.
[44] 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
[45] 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): p. 509-15.

[46] 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): p. 376-82.
[47] Komwilaisal 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): p. S34-37.
[48] Bahlmann F, Fittschen M, Reinhard I, Wellek S, Puhl A. Blood FlowVelocityWaveforms of the Umbilical Artery in a Normal Population: Reference Values from 18Weeks to 42Weeks of Gestation. Ultraschall in Med 2012; 33: E80–E87
[49] 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.
[50] 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
[51] Srikumar S, Debnath J, Ravikumar R, Bandhu HC, Maurya VK. Doppler indices of the umbilical and fetal middle cerebral artery at 18-40 weeks of normal gestation: A pilot study.Med J Armed Forces India. 2017 Jul;73(3):232-241. doi: 10.1016/j.mjafi.2016.12.008. Epub 2017 Jan 17.
[52] 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. 2018 Oct 24. doi: 10.1002/uog.20157.
[53] Boers KE[1], Bijlenga D, Mol BW, LeCessie S, Birnie E, van Pampus MG, Stigter RH, Bloemenkamp KW, van Meir CA, van der Post JA, Bekedam DJ, Ribbert LS, Drogtrop AP, van der Salm PC, Huisjes AJ, Willekes C, Roumen FJ, Scheepers HC, de Boer K, Duvekot JJ, Thornton JG, Scherjon SA. Disproportionate Intrauterine Growth Intervention Trial At Term: DIGITAT. BMC Pregnancy Childbirth. 2007 Jul 10;7:12.
[54] Lees C, Marlow N, Arabin B, Bilardo CM, Brezinka C, Derks JB, Duvekot J, Frusca T, Diemert A, Ferrazzi E, Ganzevoort W, Hecher K, Martinelli P, Ostermayer E,

Papageorghiou AT, Schlembach D, Schneider KT, Thilaganathan B, Todros T, van Wassenaer-Leemhuis A, Valcamonico A, Visser GH, Wolf H; 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. doi: 10.1002/uog.13190.
[55] 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.

Figure legends

Figure 1. Study selection process.

Figure 2. UA-PI above the 95th percentile of the most cited reference standards throughout the pregnancy.

Figure 3. MCA-PI below the 5th percentile of the most cited reference standards throughout the pregnancy.

Figure 4. CPR below the 5th percentile of the most cited reference standards throughout the pregnancy.

Figure 5. Differences between the highest and lowest UA-PI>95th percentile, MCA-PI<5th,and CPR<5th percentiles for each gestational age.

Table 1. Main characteristics of the included studies

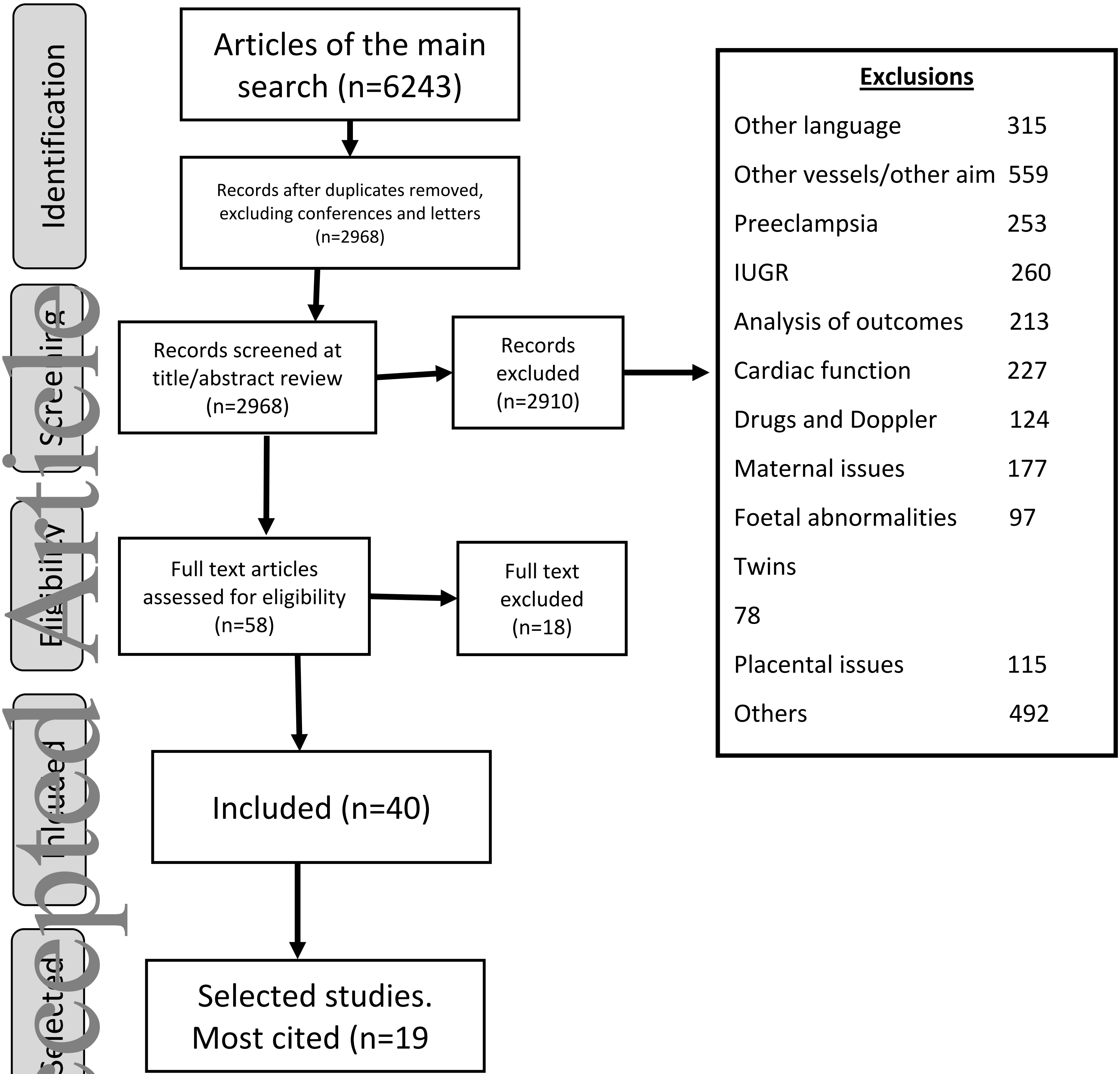
Reference	Year	Patients (n)	Scans (n)	Weeks	Study Design	No. of Citations (n)	Doppler

Arduini et al[52]	1990	1556	1556	20-42	Cross-sectional	325	UA/MCA
Baschat et al[52]	2003	306	306	20-40	Cross-sectional	199	UA/MCA/CPR
Acharya et al [52]	2004	130	513	19-41	Longitudinal	161	UA
Ebbing et al[52]	2007	161	566	21-39	Longitudinal	86	MCA/CPR
Wladimiroff et al[52]	1988	284	284	26-38	Cross-sectional	43	UA
Bahlman et al[52]	2002	926	926	18-42	Cross-sectional	59	MCA
Parra-Cordero et al[52]	2007	172	172	23-40	Cross-sectional	37	UA/MCA
Manabe et al[52]	1995	20	195	15-40	Longitudinal	16	UA
Fogarty et al[52]	1990	85	783	16-42	Longitudinal	13	UA
Tarzamni et al[52]	2009	1037	1037	20-40	Cross-sectional	9	MCA
Morales-Rosello et al[52]	2015	2323	2323	19-41	Cross-sectional	5	MCA/CPR
Medina Castro et al[52]	2006	2081	2081	20-40	Cross-sectional	5	UA
Medina Castro et al[52]	2006	727	727	20-40	Cross-sectional	4	MCA
Komwilaisak et al[52]	2004	312	312	20-37	Cross-sectional	4	MCA
Bahlman et al[52]	2012	1926	1926	18-40	Cross-sectional	3	UA/MCA
Romero et al[52]	1999	60	337	30-40	Longitudinal	0	UA
Ayoola et al[52]	2016	400	400	15-39	Cross-sectional	0	UA
Srikumar et al[52]	2017	200	773	19-40	Longitudinal	0	UA/CPR
Ciobanu et al[52]	2018	72417	72417	20-41	Cross-sectional	0	UA/CPR

Table 2. Number of small-for-gestational-age (SGA) fetuses classified as abnormal for UA-PI, MCA-PI, and CPR by the maximum and minimum published cut-off values for each gestational age. (Simulation from a cohort of 617 consecutive SGA fetuses)

	Number of SGA fetuses with abnormal Doppler	
Umbilical Artery PI	**Lowest UAPI>95 (%)**	**Highest UAPI>95 (%)**
Total* SGA (n=617)	151 (24.5%)	13 (2.1%)
SGA>37 weeks (N=90)	32 (33.7%)	2 (2.1%)
Middle Cerebral Artery PI	**Lowest MCA<5 (%)**	**Highest MCA<5 (%)**
Total SGA* (n=585)	5 (0.9%)	135 (23.1%)
SGA>37 weeks (n=90)	1 (1.1%)	12 (13.3%)
Cerebroplacental Ratio	**Lowest CPR<5 (%)**	**Highest CPR<5 (%)**
Total SGA* (n=577)	32 (5.5%)	191 (33.1%)
SGA>37 weeks (n=90)	5 (5.6%)	21 (23.3%)

** SGA fetuses from 24 to 41 weeks.*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Screening
Eligibility
Included
Selected
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Included (n=40)
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Other language 315
Other vessels/other aim 559
Preeclampsia 253
IUGR 260
Analysis of outcomes 213
Cardiac function 227
Drugs and Doppler 124
Maternal issues 177
Foetal abnormalities 97
Twins
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Placental issues 115
Others 492

Accepted Article

Figure 2. *Pulsatility index above the 95th percentile of the most cited umbilical artery reference standards throughout the pregnancy*.

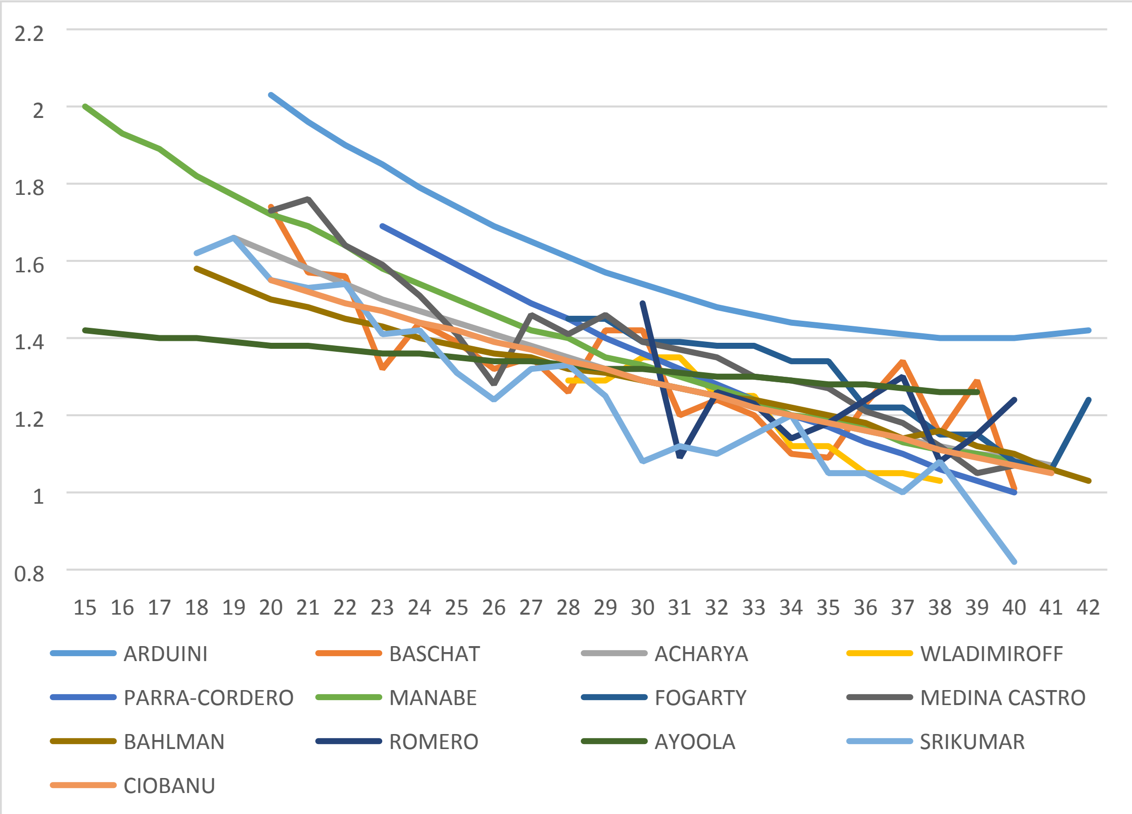

Figure 3. *Pulsatility index below the 5th percentile of the most cited middle cerebral artery reference standards throughout the pregnancy*.

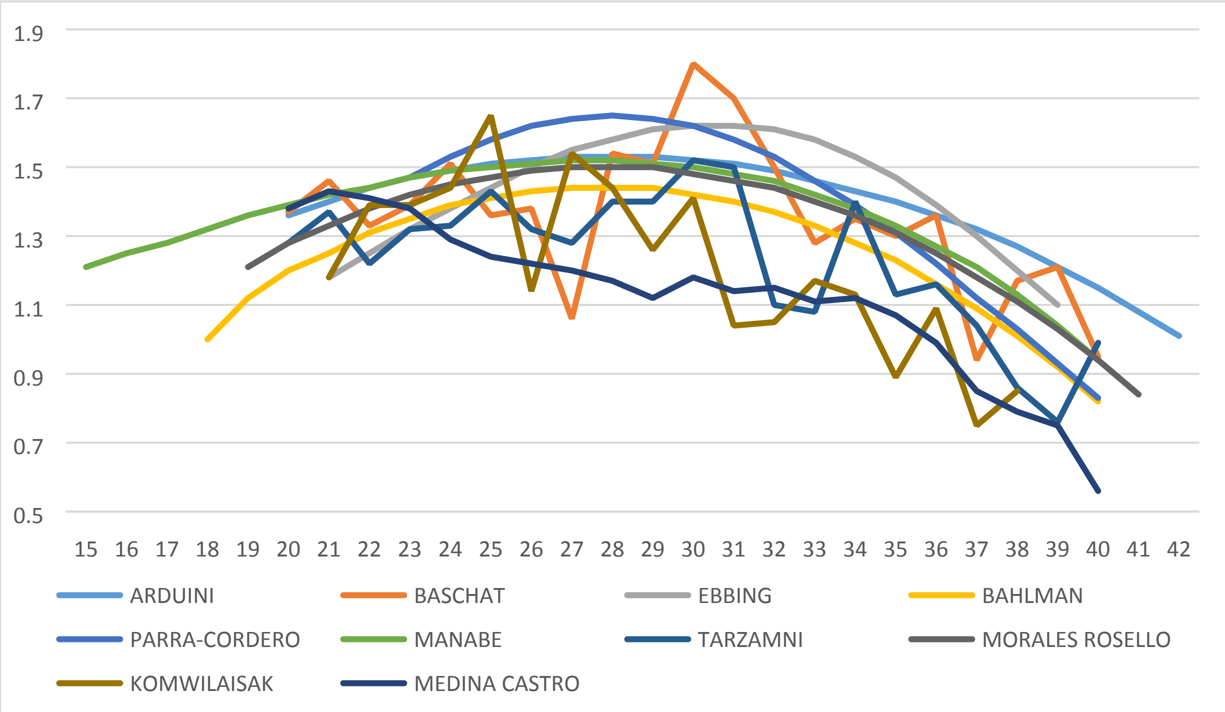

Figure 4. Pulsatility index below the 5th percentile of the most cited cerebroplacental ratio reference standards throughout the pregnancy.

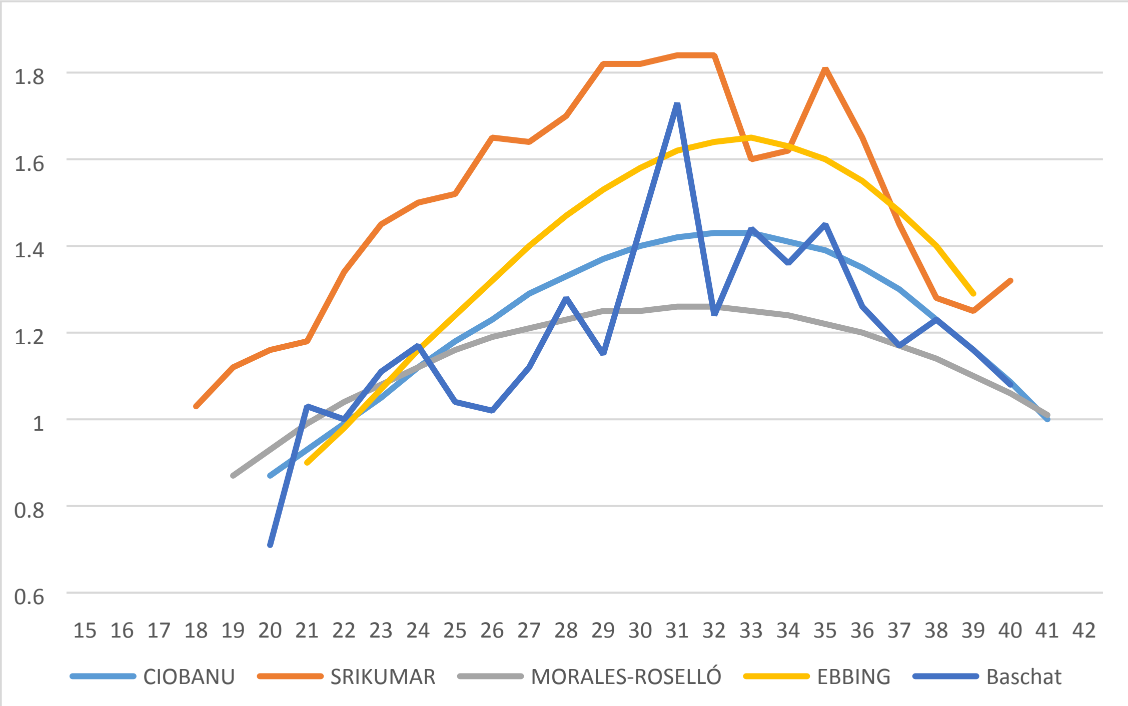

Figure 5. Differences between the highest and lowest pulsatility indices for UA>95th percentile, MCA<5th,and CPR<5th percentiles for each gestational age.