Ultrasound Obstet Gynecol 2020; **56**: 166–172
Published online 30 June 2020 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.20380

Clinical impact of Doppler reference charts on management of small-for-gestational-age fetuses: need for standardization

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KEYWORDS: cerebroplacental ratio; Doppler; Doppler reference values; fetal growth restriction; middle cerebral artery; SGA; umbilical artery

CONTRIBUTION

What are the novel findings of this work?
This study shows that the numerous reference charts for fetal Doppler proposed in the literature demonstrate significant variability in clinically relevant cut-off values. The choice of Doppler reference chart has significant clinical impact on the management of small-for-gestational-age fetuses.

What are the clinical implications of this work?
This study demonstrates the need to create a new Doppler reference chart in a study with high methodological quality since there are substantial differences in the references reported in the published literature, which impact on decisions in clinical practice.

ABSTRACT

Objective *To assess clinical variability in the management of small-for-gestational-age (SGA) fetuses according to different published Doppler reference charts for umbilical artery (UA) and fetal middle cerebral artery (MCA) Doppler indices and cerebroplacental ratio (CPR).*

Methods *We performed a systematic search of MEDLINE, EMBASE, CINAHL and the Web of Science databases from 1954 to 2018 for studies with the sole aim of creating fetal Doppler reference values for UA, MCA and CPR. The top cited articles for each Doppler parameter were included. Variability in Doppler values at the following clinically relevant cut-offs was assessed: UA-pulsatility index (PI) > 95^{th} percentile; MCA-PI < 5^{th} percentile; and CPR < 5^{th} percentile. Variability was calculated for each week of gestation and expressed as the percentage difference between the highest and lowest Doppler value at the clinically relevant cut-offs. Simulation analysis was performed in a cohort of SGA fetuses (n = 617) to evaluate the impact of this variability on clinical management.*

Results *From a total of 40 studies that met the inclusion criteria, 19 were analyzed (13 for UA-PI, 10 for MCA-PI and five for CPR). Wide discrepancies in reported Doppler reference values at clinically relevant cut-offs were found. MCA-PI showed the greatest variability, with differences of up to 51% in the 5^{th} percentile value at term. Variability in the 95^{th} percentile of UA-PI and the 5^{th} percentile of CPR at each gestational week ranged from 21% to 41% and 15% to 33%, respectively. As expected, on simulation analysis, these differences in Doppler cut-off values were associated with significant variation in the clinical management of SGA fetuses, despite using the same protocol.*

Conclusions *The choice of Doppler reference chart can result in significant variation in the clinical management of SGA fetuses, which may lead to suboptimal outcomes and inaccurate research conclusions. Therefore, an attempt to standardize fetal Doppler reference ranges is needed. Copyright © 2019 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Fetal growth restriction (FGR) is a major cause of perinatal morbidity and mortality[1]. Apart from close monitoring during pregnancy and delivery, there are no other evidence-based treatments for suspected

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Accepted: 17 June 2019

growth-restricted fetuses to ensure a healthy neonate that is not premature[2,3]. At present, ultrasound plays a critical role in the clinical management of FGR fetuses[4,5], and estimated fetal weight (EFW) by ultrasound is the gold standard for the diagnosis of FGR[6]. Nevertheless, Doppler measurement of fetal cardiovascular function is the basis for the schedule of monitoring and optimum timing of delivery[7].

The methodology for fetal Doppler evaluation has been standardized[8]. Despite some controversy[9], hemodynamic patterns of progression in early and late FGR fetuses are well described[10–13]. Qualitative changes in umbilical artery (UA) Doppler parameters, such as absent or reversed end-diastolic flow, clearly indicate an increased risk of fetal demise[2–5]. However, the association between sparing of the fetal brain, as assessed using UA pulsatility index (PI), fetal middle cerebral artery (MCA)-PI and cerebroplacental ratio (CPR), and perinatal and long-term outcomes has not been well determined[14–17]. Given the large number of published Doppler references, it could be hypothesized that this lack of evidence may be explained partially by heterogeneity in the different Doppler standards used.

In a recent systematic review, we showed that there is considerable methodological heterogeneity in studies reporting reference ranges for UA and MCA Doppler indices and CPR[18]. The probable reason for these differences is methodological issues as, in the 38 included studies, 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 there was a lack of blinding of measurements in all but one study. It was evident from this review that differences between reference charts would have important implications for clinical practice.

In the present study, we aimed to quantify the effect of these differences in a clinical setting by analyzing the potential heterogeneity of the most frequently used published Doppler reference charts for UA-PI, MCA-PI and CPR, and assessing the influence of this 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 UA-PI, MCA-PI and CPR. The search strategy was designed by a professional information specialist and included studies reported from January 1954 to 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 with the sole aim of establishing normal values between 20 and 40 weeks' gestation were considered. The number of citations that each study had received, as of 8 March 2019, was obtained from the Web of Knowledge[19]. The 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 (S.R.-M. and D.O.) to determine study inclusion. Disagreements were resolved through consensus with a third reviewer (A.T.P.). In accordance with our objective to determine the clinical impact of variability, we selected the Doppler references most used in clinical practice and research. Thus, we selected the 10 most cited studies for each Doppler variable to compare the most used published Doppler reference standards. UA-PI $> 95^{th}$ percentile, MCA-PI $< 5^{th}$ percentile and CPR $< 5^{th}$ percentile were considered to be the clinically relevant cut-offs[4,5,7]. If these clinical cut-offs were not reported by the authors, they were calculated using the mean and SD for gestational age[21,22]. Variability in clinically relevant cut-off values was expressed as a percentage and was obtained by subtracting the lowest Doppler value from the highest and dividing by the highest Doppler value for each week of gestation.

Finally, simulation analysis was performed in a cohort of 617 consecutive SGA fetuses, defined as EFW $< 10^{th}$ percentile[23], assessed in our center from 24–41 weeks' gestation. FGR was defined as EFW $< 10^{th}$ percentile and any abnormal Doppler variable (UA-PI $> 95^{th}$ percentile, MCA-PI $< 5^{th}$ percentile or CPR $< 5^{th}$ percentile), with induction of labor recommended at 37 weeks[4,5,7].

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

Statistical analysis was performed using Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, USA) and IBM SPSS Statistics v. 20 (SPSS, Armonk, NY, USA).

RESULTS

The database searches yielded 6243 citations; Figure 1 summarizes the inclusion of studies. Forty studies met the inclusion criteria, having a sole objective of determining reference Doppler values. We included the top 10 most cited Doppler reference values for MCA-PI, but we included the top 13 most cited UA-PI Doppler reference ranges instead of 10 to avoid selection bias, because four articles on UA-PI references had the same number of citations. We found only five articles presenting reference ranges for CPR. Table 1 describes the main characteristics and number of citations of the 19 selected studies[24–42].

The distribution of 95^{th} percentile values for UA-PI and 5^{th} percentile values for MCA-PI and CPR among all pregnancies in each study is plotted in Figure 2. Notably, substantial variability existed between the reference values for the different UA-PI, MCA-PI and CPR cut-offs. Furthermore, many of the included studies showed an anomalous distribution of cut-off values during gestation, possibly owing to inappropriate statistical analyses[18].

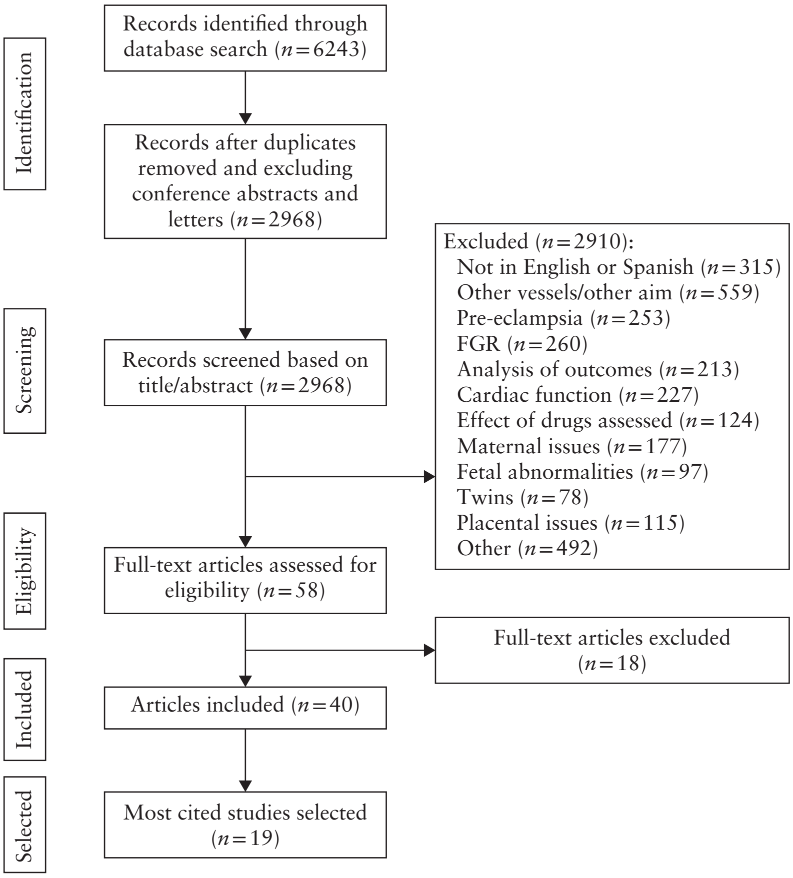

Figure 1 Flowchart summarizing inclusion of studies reporting fetal Doppler reference ranges for umbilical artery, middle cerebral artery and cerebroplacental ratio. FGR, fetal growth restriction.

Table 1 Characteristics of included studies reporting fetal Doppler reference ranges

Study	*Patients* (n)	*Scans* (n)	*GA range (weeks)*	*Study design*	*Citations** (n)	*Doppler variables examined*
Arduini (1990)[24]	1556	1556	20–42	Cross-sectional	325	UA-PI, MCA-PI
Baschat (2003)[25]	306	306	20–40	Cross-sectional	199	UA-PI, MCA-PI, CPR
Acharya (2005)[26]	130	513	19–41	Longitudinal	161	UA-PI
Ebbing (2007)[27]	161	566	21–39	Longitudinal	86	MCA-PI, CPR
Wladimiroff (1988)[28]	284	284	26–38	Cross-sectional	43	UA-PI
Bahlmann (2002)[29]	926	926	18–42	Cross-sectional	59	MCA-PI
Parra-Cordero (2007)[30]	172	172	23–40	Cross-sectional	37	UA-PI, MCA-PI
Manabe (1995)[31]	20	195	15–40	Longitudinal	16	UA-PI, MCA-PI
Fogarty (1990)[32]	85	783	16–42	Longitudinal	13	UA-PI
Tarzamni (2009)[33]	1037	1037	20–40	Cross-sectional	9	MCA-PI
Morales-Roselló (2015)[34]	2323	2323	19–41	Cross-sectional	5	MCA-PI, CPR
Medina Castro (2006)[35]	2081	2081	20–40	Cross-sectional	5	UA-PI
Medina Castro (2006)[36]	727	727	20–40	Cross-sectional	4	MCA-PI
Komwilaisak (2004)[37]	312	312	20–37	Cross-sectional	4	MCA-PI
Bahlmann (2012)[38]	1926	1926	18–40	Cross-sectional	3	UA-PI
Romero Gutiérrez (1999)[39]	60	337	30–40	Longitudinal	0	UA-PI
Ayoola (2016)[40]	400	400	15–39	Cross-sectional	0	UA-PI
Srikumar (2017)[41]	200	773	19–40	Longitudinal	0	UA-PI, CPR
Ciobanu (2019)[42]	72 417	72 417	20–41	Cross-sectional	0	UA-PI, CPR

Only first author is given for each study. *As of 8 March 2019. CPR, cerebroplacental ratio; GA, gestational age; MCA-PI, middle cerebral artery pulsatility index; UA-PI, umbilical artery pulsatility index.

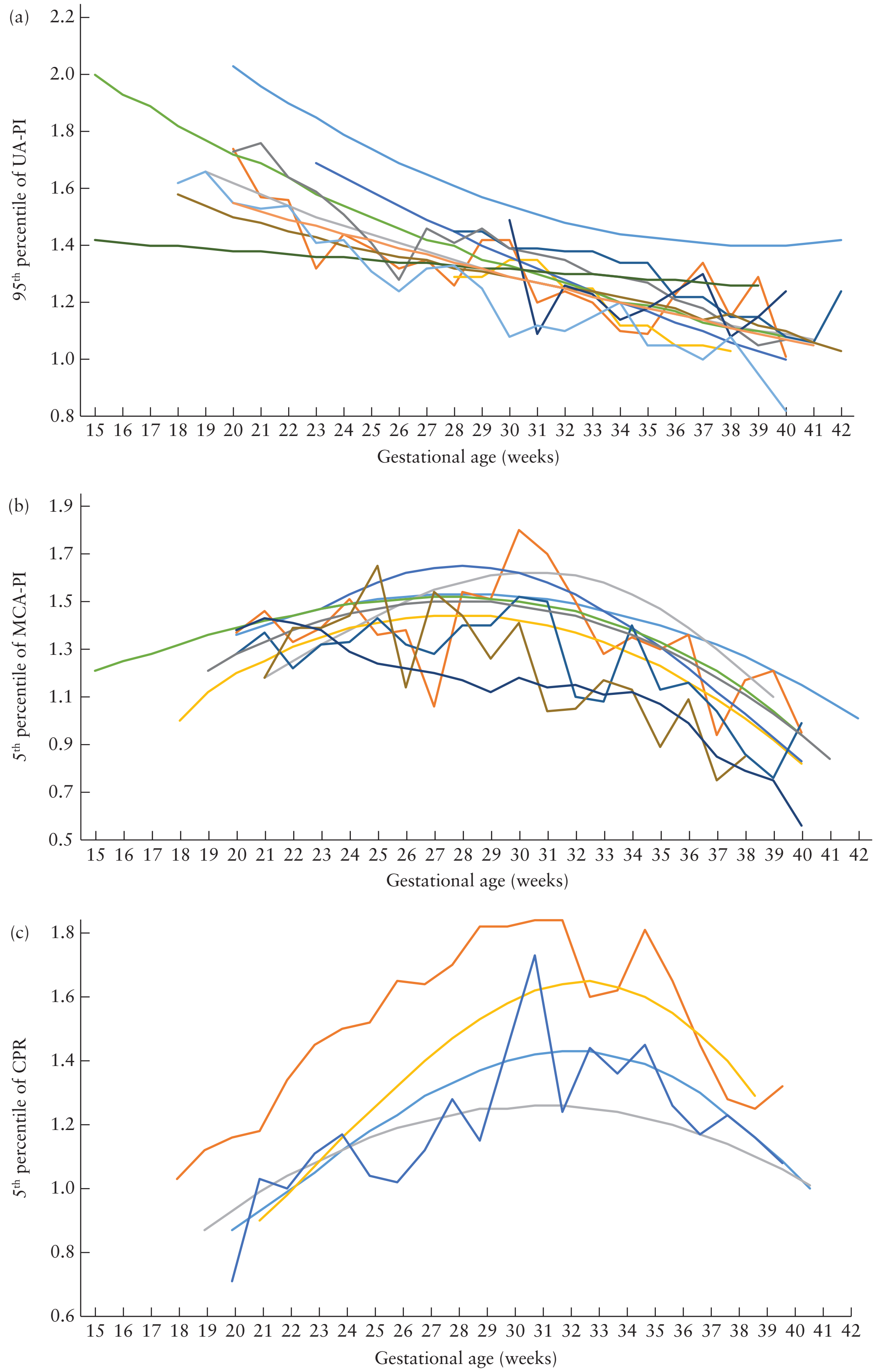

Figure 2 Distribution of 95th percentile of umbilical artery (UA) pulsatility index (PI) (a), 5th percentile of middle cerebral artery (MCA)-PI (b) and 5th percentile of cerebroplacental ratio (CPR) (c) of most cited fetal Doppler reference standards, according to gestational age. Only first author is given. (a) —, Arduini (1990)[24]; —, Baschat (2003)[25]; —, Acharya (2005)[26]; —, Wladimiroff (1988)[28]; —, Parra-Cordero (2007)[30]; —, Manabe (1995)[31]; —, Fogarty (1990)[32]; —, Medina Castro (2006)[35]; —, Bahlmann (2012)[38]; —, Romero Gutiérrez (1999)[39]; —, Ayoola (2016)[40]; —, Srikumar (2017)[41]; —, Ciobanu (2019)[42]. (b) —, Arduini (1990)[24]; —, Baschat (2003)[25]; —, Ebbing (2007)[27]; —, Bahlmann (2002)[29]; —, Parra-Cordero (2007)[30]; —, Manabe (1995)[31]; —, Tarzamni (2009)[33]; —, Morales-Roselló (2015)[34]; —, Komwilaisak (2004)[37]; —, Medina Castro (2006)[36]. (c) —, Ciobanu (2019)[42]; —, Srikumar (2017)[41]; —, Morales-Roselló (2015)[34]; —, Ebbing (2007)[27]; —, Baschat (2003)[25].

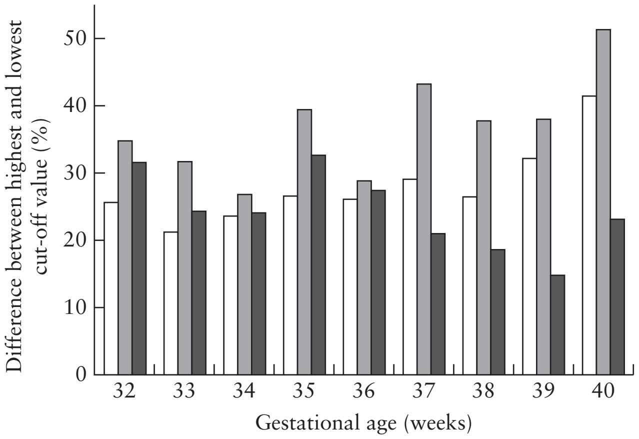

Figure 3 Percentage difference between highest and lowest 95th percentile values of umbilical artery pulsatility index (PI) (□) (a), 5th percentile values of middle cerebral artery PI (▩) (b) and 5th percentile values of cerebroplacental ratio (■) (c) of most cited fetal Doppler reference standards, according to gestational age.

Table 2 Proportion of small-for-gestational-age (SGA) fetuses with abnormal umbilical artery (UA) pulsatility index (PI), middle cerebral artery (MCA)-PI or cerebroplacental ratio (CPR), according to whether highest or lowest published cut-off value is used

		Doppler cut-off value	
Doppler variable	n	*Lowest* *(n (%))*	*Highest* *(n (%))*
UA-PI > 95th percentile			
SGA overall*	617	151 (24.5)	13 (2.1)
SGA > 37 weeks	90	32 (35.6)	2 (2.2)
MCA-PI < 5th percentile			
SGA overall*	585	5 (0.9)	135 (23.1)
SGA > 37 weeks	90	1 (1.1)	12 (13.3)
CPR < 5th percentile			
SGA overall*	577	32 (5.5)	191 (33.1)
SGA > 37 weeks	90	5 (5.6)	21 (23.3)

Simulation analysis based on cohort of 617 consecutive SGA fetuses. *SGA fetuses from 24 to 41 weeks.

Variability, expressed as the percentage difference between the highest and lowest value at each week of gestation for the 95th percentile of UA-PI and the 5th percentiles of MCA-PI and CPR, is shown in Figure 3. The mean difference between the highest and lowest values for the 95th percentile of UA-PI for each completed gestational week was 28.02% (range, 21–41%). Variability was more marked for the 5th percentile of MCA-PI, with a mean difference of 36.86% (range, 26.8–51.3%). These differences increased after 35 weeks' gestation, at which point the presence of abnormal MCA-PI has important implications for clinical management. Finally, the 5th percentile of CPR presented the lowest variability, with a mean difference of 24.09% (range, 15–32.6%). Again, as expected, the highest variability in CPR was seen at term.

To evaluate the potential impact of the variability among Doppler 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 lowest or highest value for the 95th percentile of UA-PI and those for the 5th percentiles of MCA-PI and CPR for each gestational week, the proportion of SGA fetuses classified as growth restricted based on the presence of abnormal UA-PI, MCA-PI and CPR varied from 24.5% to 2.1%, 0.9% to 23.1% and 5.5% to 33.1%, respectively. According to several clinical guidelines[4,5], induction of labor may be required for UA-PI > 95th percentile, MCA-PI < 5th percentile or CPR < 5th percentile at full term. Even following the same clinical protocol, the potential proportion of labor inductions in pregnancies with a SGA fetus at term could vary from 2.2% to 35.6%, 1.1% to 13.3% and 5.6% to 23.3%, depending on the reference range for UA-PI, MCA-PI and CPR used, respectively.

DISCUSSION

This is the first systematic review to analyze the impact of variability among the most frequently used Doppler reference charts for UA-PI, MCA-PI and CPR on the clinical management of SGA fetuses.

In most cases, fetal growth restriction is thought to be a marker of uteroplacental insufficiency[43]. Angiogenic defects that result in placental pathology are referred to collectively as maternal vascular lesions of underperfusion[44]. Hence, UA-PI can reflect indirectly the dimensions of the villous vascular tree, blood-flow resistance in the fetal compartment of the placenta and the relative risk of nutritional and metabolic deficiency[45,46]. Furthermore, a growing body of evidence suggests that MCA-PI, alone or in combination with UA-PI (i.e. CPR), may be helpful in identifying fetuses at risk of FGR[47–49], 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 tools for monitoring and decision-making for SGA fetuses[4,5]. UA-PI vasoconstriction is defined according to a statistical cut-off of the 95th percentile[50]. Similarly, the 5th percentile of MCA-PI or CPR defines brain vasodilation[50]. Therefore, appropriate Doppler reference values are needed to accurately estimate these cut-off points. However, a systematic review published recently by our group revealed considerable methodological heterogeneity in studies reporting reference ranges for UA-PI, MCA-PI and CPR[18]. In the present study, we showed large differences among fetal Doppler reference charts in clinically relevant cut-off values.

For our analysis, we selected the most frequently cited studies in the literature to represent the most used ranges for clinical practice and research purposes. The methodological quality criteria for studies providing reference values have been described previously[18,51]. However, all studies 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 (those of Arduini and Rizzo[24], Baschat and Gembruch[25] and Acharya *et al.*[26]) show an important risk of bias owing to the fact that they are 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 studies are more likely to be cited than are more recent ones with higher-quality methodology because the results of newer studies might not have had sufficient time to be incorporated into clinical practice[52].

We found important sources of bias in the most widely used studies[18]; ultrasound examinations were not performed for research purposes[24,25,28,30,33,34,40], neither the recruitment period[24,25,27–29,31,32,34,38] nor perinatal results[24] were described, or the study was performed at a single center[24–31,37,39]. We also found a lack of reporting of necessary sample sizes[24,26,28–31,34–36,38,40], gestational-age dating method[25–28,31,40], experience of the sonographers[24,26–28,31,33,34,39,40] and even the inclusion and exclusion criteria[26,28,29,31,34,39] and quality controls[24–31,33–40]. As shown in Figure 2, an irregular distribution was observed among the cut-off values according to gestational age in many of the analyzed reference ranges, suggesting inappropriate statistical treatment of the data.

Identification of the risk of adverse fetal outcome is a challenge in perinatal medicine. The main objective of close monitoring of FGR fetuses is to deliver a healthy neonate without extreme prematurity, while other objectives are to avoid 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 showed clearly that the use of inaccurate tools can lead to inaccurate decision-making for important clinical issues. Optimal timing of delivery of SGA fetuses is one of the main focuses of FGR research[2,3,53]. According to our results, even with the use of a standardized clinical protocol, the Doppler reference chart used has significant clinical impact. For example, the rate of induction at term could range from 2.2% to 35.6% when based on UA-PI, 1.1% to 13.3% when based on MCA-PI and 5.6% to 22.3% when based on CPR. Notably, the broadest variation in Doppler cut-off values is at full term, which is a critical time for clinical decision-making. From our point of view, this potential variability in the clinical management of SGA fetuses is unacceptable.

Strengths and weaknesses

The main strength of this study is the rigorous methodology used; we performed a comprehensive systematic review including a relatively large number of studies. A limitation of the study is that the evaluation of the impact of Doppler reference charts in clinical management was performed in a retrospective cohort of SGA fetuses using specific Doppler references that determined our clinical protocol at that time. Thus, our results could potentially be biased. Owing to the high number of published Doppler value reference charts, it is unlikely that a prospective study with a similar aim has been conducted. Another potential limitation is the inclusion of studies published only in English or Spanish. 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 on year of publication because some of the older ultrasound Doppler charts are still used in current clinical practice. Apart from PI, other parameters such as systolic/diastolic ratio (S/D) are sometimes used for the management SGA fetuses. We did not analyze such parameters for two reasons: firstly, only three of the most cited published Doppler references (Ayoola *et al.*[40], Acharya *et al.*[26] and Fogarty *et al.*[32]) give reference ranges for UA-S/D ratio, and one (Tarzamni *et al.*[33]) mentions MCA-S/D ratio; secondly, as we did not have data on S/D ratio from the cohort of SGA fetuses that was used to perform the simulation analysis, this variable could not be included. Although this is a potential limitation, the relationship that exists between PI, resistance index and S/D ratio means that the principle of reaching different clinical decisions depending on the reference chart used still applies.

The choice of Doppler reference chart is associated with significant variation in the clinical management of SGA fetuses, which may lead to suboptimal outcomes and inaccurate research conclusions. In conclusion, an attempt to standardize fetal Doppler reference ranges is needed.

ACKNOWLEDGMENTS

A.T.P. is supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC). D.O. is supported by the Instituto de Salud Carlos III (Government of Spain), through a mobility grant and intensification program for researchers and Red de Salud Materno Infantil y del Desarrollo (SAMID), RETICS. Instituto de Salud Carlos III (ISCIII), Subdirección General de Evaluación y Fomento de la Investigación y Fondo Europeo de Desarrollo Regional (FEDER) Ref: RD12/0026. We would like to thank Nia Roberts, an outreach librarian at the Bodleian Health Care Libraries, for her assistance in the literature search.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Search strategy (* indicates keyword truncation)