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Effect of Maternal and Fetal Characteristics in Feto-Placental Doppler and Impact of Using Adjusted Standards in the Definition of Fetal Growth Restriction at Term

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Keywords
Doppler standards · Fetal growth restriction · Small for gestational age · Cerebroplacental ratio · Umbilical artery Doppler · Adjusted Doppler standards

Abstract
Introduction: This study aimed to determine the effect and clinical impact of physiological characteristics on the 95th/5th centile of the umbilical artery (UA) Doppler and the cerebroplacental ratio (CPR), at 36+ weeks. ***Methods:*** From the multicenter randomized trial "Ratio37," we selected 4,505 low-risk pregnant women between June 2016 and January 2020. We registered physiological characteristics and the pulsatility indexes (PI) of the UA and middle cerebral artery (36–39 weeks). The 95th/5th centile of the UA PI and CPR was modeled by quantile regression. To evaluate the clinical impact of adjusting Doppler, we retrospectively applied gestational age (GA) and fully adjusted standards to 682 small for gestational age (SGA)-suspected fetuses (37 weeks) from a cohort of consecutive patients obtained between January 2010 and January 2020. ***Results:*** Several physiological characteristics significantly influenced the 95th/5th centile of the UA and CPR PI. The fully adjusted 95th centile of the UA was higher, and the 5th centile of the CPR was lower than GA-only-adjusted standards. Of the 682 SGA fetuses, 150 (22%) were classified as late fetal growth restricted only by GA and 112 (16.4%) when we adjusted Doppler. These 38 fetuses had similar perinatal outcome than the SGA group. ***Discussion:*** The 95th/5th centile of the UA and CPR PI is significantly influenced by physiological characteristics. Adjusting Doppler standards could differentiate better between FGR and SGA.

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Introduction

The evaluation of fetal Doppler in small for gestational age (SGA) fetuses is an accepted clinical tool for decision-making [1]. An international consensus exists on the diagnosis of late fetal growth restriction (FGR), as opposed to (constitutional) SGA, including biometrical (below the 3rd centile or declining growth) and Doppler (umbilical artery [UA] and the cerebroplacental ratio [CPR]) criteria [2].

Many different reference ranges for the UA and the CPR have been published in the last 20 years [3–7], all showing considerable heterogeneity and lack of methodological criteria [8]. The variability among the published references reaches 41% for the 95th centile of the UA and 33% for the 5th centile of the CPR [8]. The clinical consequence of these discrepancies is a significant variation in SGA fetus clinical management, even when using the same protocol, which may lead to suboptimal outcomes.

In addition to methodological issues as a source of variability between the published references, differences in the population's baseline characteristics from which they were derived may also explain these discrepancies. The importance of only including low-risk pregnancies to obtain prescriptive (as opposed to merely descriptive) references has been highlighted [9]. However, even among healthy pregnancies, some physiological maternal and fetal characteristics may also account for part of the variability. We and others have described the influence of maternal and fetal factors on the fetal Doppler parameters [10]. We are not aware of any study evaluating the clinical impact of using adjusted (i.e., adjusted for maternal and fetal characteristics) versus traditional gestational age (GA)-adjusted-only Doppler standards on the identification of FGR at term, when labor induction is recommended after this diagnosis [11].

This study aims to determine the effect of maternal and fetal physiological characteristics on the thresholds used in clinical practice to define term FGR, derived from a large population of low-risk pregnancies. Furthermore, we sought to evaluate the clinical impact that the use of these adjusted standards has on identifying term FGR in a cohort of SGA fetuses evaluated at term.

Material and Methods

Study Population

Construction Cohort

The Ratio37 trial is an ongoing randomized, open-label, multicenter controlled study in which low-risk pregnancies are recruited, and umbilical and middle cerebral artery Doppler measurements are performed at 37 weeks in a concealed versus revealed design [12]. In the concealed group, management adheres to the current standard of care for managing SGA pregnancies. In the revealed group, CPR data obtained from Doppler evaluation are integrated into the criteria used for decision regarding labor induction.

Inclusion criteria were singleton, low risk (absence of any medical and obstetrical pathological condition), and nonsmoking at booking pregnant women from 5 countries (Hospital de Especialidades del Niño y la Mujer, Querétaro Mexico; Hospital Universitario, Santiago, Chile; Hospital Clinic and Hospital del Mar, Barcelona, Spain; University Hospital Olomouc and Obstetrics and Gynecology Institute for the care of Mother and Child, Prague, Czech Republic; St Sophia's Specialist Hospital, Warsaw, Poland) between June 2016 and February 2020. For this study, we excluded fetuses with an abnormal karyotype, structural abnormalities, congenital infections, and with an estimated fetal weight (EFW) <10th centile [13]. All pregnancies were ultrasound dated, using the crown-rump length measurement before 14 weeks [14]. All women gave their signed consent, and each local ethics committee approved the study protocol.

Testing Cohort

We constructed a retrospective cohort of consecutive patients referred between January 2010 and January 2020 to a single center (Barcelona Center for Maternal-Fetal and Neonatal Medicine) for suspected SGA (EFW <10th centile) [15] diagnosed after 32 weeks of pregnancy and delivered after 37 weeks of pregnancy. Exclusion criteria were an EFW below the 3rd centile at the last evaluation before delivery. This cohort has been described in detail elsewhere [16].

Measurements

In all women of the construction cohort, we performed a Doppler evaluation at 36.0–38.6 weeks. Images of the Doppler measurements were systematically stored in digital imaging and communications in medicine format and subjected to quality audits. Doppler measurements were performed adhering to the International Society of Obstetrics and Gynecology (ISUOG) [1]. Since this is a multicenter study, the Doppler measurements were performed by a different range of experienced and specifically trained professionals (fetal-maternal medicine specialists, sonographers, and ultrasound technicians) working with different ultrasound machines (GE Voluson E8 Expert, 730 Pros, Siemens S3000, and Aloka Prosound F75). During the study's conduction, an image quality control was carried out based on an objective scoring method published in 2020 [17], obtaining over 85% of images rated as perfect or almost perfect [18]. We performed at least 3 measures per fetus per scan. Ultrasound data were prospectively collected and registered in all participating centers. We adhered to the Doppler diagnostic criteria for term FGR of the Delphi consensus [2]: UA pulsatility index (PI) >95th centile or a CPR <5th centile.

Outcomes

The primary endpoint was a composite adverse outcome, defined as caesarean section for fetal nonreassuring status, metabolic acidosis (UA pH < 7.10 and a base excess >−12 mEq/L in the newborn), 5-min Apgar score <7, admission to the neonatal unit, or perinatal death. Secondary neonatal outcomes were neonatal

Table 1. Baseline characteristics of the included cohorts

	Construction cohort	Testing cohort
N	4,505	682
Parity		
Nulliparity	2,313 (51.3)	427 (62.5)
1	1,671 (37.1)	200 (29.3)
2+	521 (11.6)	55 (8.1)
Non-White ethnicity	1,283 (28.5)	176 (25.8)
Maternal age at delivery, years^	31.6 (4.8); 18–44	31.6 (6.2)
Maternal weight at booking, kg^	64.6 (11.7); 39–152	57.8 (11)
Maternal height, cm^	164 (7.2); 140–190	160.5 (5.9)
Low socioeconomic level†	733 (16.3)	184 (27)
Smoking	0	571 (83.7)
1–10 cigarettes/day	0	98 (14.4)
11+ cigarettes/day	0	13 (1.9)
Alcohol consumption >170 g/week	0	4 (0.6)
Active recreational drug consumption	0	8 (1.2)
Pregestational diabetes	0	19 (2.8)
Chronic hypertension	0	14 (2.1)
Gestational age at last scan^	36.8 (0.6); 36–38.9	38.2 (37–41.4)
EFW* at last scan^	2,936 (309); 2,255–4,505	2,516 (208); 1,712–3,020
EFW* centile at last scan^	62.3 (25.4); 10–100	5 (2.1); 3–9.9

^ Data shown as mean (SD) and range. * EFW (estimated fetal weight). †Routine occupations, long-term unemployment, or never worked (UK National Statistics Socioeconomic Classification).

hypoglycemia defined as a plasma glucose level of <30 mg/dL in the first 24 h of life and neonatal hyperbilirubinemia defined as a total serum bilirubin level above 5 mg per dL (86 µmol per L).

Statistical Analysis

In the construction cohort, we derived the 95th centile of the UA PI and the 5th centile of the CPR by quantile regression, as described by Wei et al. [19]. Quantile regression estimates the distribution directly by fitting a function to each chosen quantile using linear programming, without distributional assumptions. Besides, quantile regression is more robust against the influence of outliers in the data. In the first model (GA-only-adjusted), we smoothed the estimated quantiles by a function of GA. In the second model (fully adjusted), we further adjusted the centiles by maternal age and weight at booking, height, nulliparity (no previous deliveries above 22 weeks), white-European ethnicity (self-reported), fetal sex, and z-score of EFW. Goodness-of-fit was assessed by the procedure reported by Koenker et al. [20].

In the testing cohort, GA-only-adjusted and fully adjusted standards were applied to all pregnancies at their last evaluation before delivery (37^{+0}) and classified as SGA or term FGR by both standards. For the fully adjusted classification, the coefficient for EFW was nullified (i.e., imputed to 0 *z*-score).

χ^2 or Student *t* tests were used to evaluate differences between groups. For all the statistical analysis, R software version 2.15.1 (The R Foundation for Statistical Computing; quantreg package 5.05) was used.

Results

For the construction cohort, we included a total of 4,918 patients, of which 413 (8.4%) were excluded for an EFW <10th centile, leaving 4,505 pregnancies for the analysis. For the testing cohort, we evaluated a total of 1,037 SGA-suspected pregnancies at 37^{+} weeks, of which 355 were excluded because EFW was < 3rd centile, leaving 682 pregnancies for the analysis.

Table 1 shows the baseline characteristics of the construction and testing cohorts. Table 2 details the effect of maternal and fetal characteristics on the 95th centile of the UA and the 5th centile of the CPR.

In the construction cohort (n = 4,505), 212 (4.7%) pregnancies had a UA PI above the 95th centile as per GA-only-adjusted standards; it was 220 (4.9%) as per fully adjusted standards. Regarding the 5th centile of the CPR, 227 (5%) pregnancies had a value below this threshold as per GA-only-adjusted standards and 222 (4.9%) as per fully adjusted standards.

On average, in the testing cohort, the fully adjusted 95th centile of the UA was 0.07 units higher (95% CI: 0.065–0.068) than the same GA-only-adjusted centile. The fully adjusted 5th centile of the CPR was, on average,

Table 2. Parameters of the derived models and effect of maternal and fetal characteristics on the Doppler centiles

Parameter	Model	Coefficient	SE	p value
Umbilical artery PI (95th centile)	GA-adjusted (pseudo R^2 0.14%)			
	Intercept	0.819	0.299	0.006
	GA* at scan	0.008	0.008	0.344
	Adjusted (pseudo R^2 12.7%)			
	Intercept	0.769	0.284	0.007
	GA at scan, weeks	0.017	0.007	0.013
	Maternal height at booking, kg	−0.002	0.001	<0.001
	Maternal weight, cm	0.000	0.000	0.322
	Maternal age at scan (completed years)	0.002	0.001	0.014
	Nulliparity	0.020	0.009	0.031
	White-European ethnicity	−0.007	0.009	0.439
	Fetal female sex	0.021	0.009	0.030
	EFW* z-score	−0.030	0.004	<0.001
Cerebroplacental ratio (5th centile)	GA-adjusted (pseudo R^2 1.8%)			
	Intercept	7.273	0.613	<0.001
	GA at scan	−0.160	0.017	<0.001
	Adjusted (pseudo R^2 13.3%)			
	Intercept	6.572	0.703	<0.001
	GA at scan, weeks	−0.158	0.017	<0.001
	Maternal height at booking, kg	0.0038	0.002	0.012
	Maternal weight, cm	−0.00015	0.001	0.845
	Maternal age at scan (completed years)	−0.00032	0.002	0.876
	Nulliparity	−0.034	0.021	0.110
	White-European ethnicity	0.036	0.024	0.133
	Fetal female sex	0.013	0.022	0.551
	EFW z-score	0.043	0.011	<0.001

* GA, gestational age; EFW, estimated fetal weight; SE, standard deviation.

0.027 (0.025–0.029) lower than the same GA-only-adjusted centile.

Table 3 shows in the testing cohort the classification as SGA/FGR by both standards. Of note, of the 150 fetuses classified as term FGR by GA-only-adjusted standards, 38 (25.3%) were reclassified as SGA by using the fully adjusted Doppler standards.

Table 4 depicts the perinatal outcome by FGR classification: SGA by GA-adjusted standards, FGR only by GA-adjusted standards, and FGR by both GA-adjusted and fully adjusted standards. Of note, the perinatal outcome did not differ between the FGR only by GA-adjusted standards and the SGA groups.

Table 3. Classification according to GA-adjusted standards and adjusted standards

	GA-adjusted standards		Total
	SGA	*term FGR*	
UA PI >95th centile			
Adjusted standards			
SGA	567	45	612
Term FGR	0	70	70
Subtotal	567	115	682
CPR <5th centile			
Adjusted standards			
SGA	608	6	614
Term FGR	1	67	68
Subtotal	609	73	682
Any abnormal			
Adjusted standards			
SGA	531	38	569
Term FGR	1	112	113
Total	532	150	682

GA, gestational age; SGA, small for GA, gestational age; FGR, fetal growth restriction; UA, umbilical artery; CPR, cerebroplacental ratio; PI, pulsatility index.

Discussion

The concept of adjusting fetal weight standards for maternal and fetal characteristics known to have a physiological influence on growth is well known. However, we understand fetal Doppler as a universal and nonadjustable measure. Traditionally, reference ranges

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Table 4. Perinatal outcome by classification group

	SGA	Term FGR only by GA-adjusted standards	Term FGR by both standards	*p* value[1]	*p* value[2]
N	532	38	112		
Pre-eclampsia	20 (3.8)	1 (2.6)	9 (8)	0.71	0.052
Gestational age at delivery, weeks	39.2 (1.1); 37–42	39 (1.1); 37–41	38.4 (1.1); 37–41	0.279	<0.001
Birth weight, g	2,623 (260); 1,790–3,400	2,606 (242); 2,156–3,270	2,457 (275); 1,920–3,410	0.696	<0.001
Birth weight centile	6.3 (7.5); 0–49	8.4 (10.9); 0–47	5.2 (9.5); 0–48	0.108	0.18
Birth weight centile < p10	430 (80.8)	27 (71.1)	100 (89.3)	0.148	0.032
Birth weight centile < p3	225 (42.3)	16 (42.1)	62 (55.4)	0.98	0.011
Labor induction	340 (63.9)	17 (44.7)	63 (56.3)	0.018	0.131
Caesarean section	135 (25.5)	13 (34.2)	49 (43.8)	0.238	<0.001
CS for NRFS	81 (15.2)	5 (13.2)	27 (24.1)	0.739	0.022
5-min Apgar score <7	2 (0.4)	1 (2.6)	1 (0.9)	0.076	0.490
Neonatal metabolic acidosis	8 (1.5)	0	2 (1.8)	0.448	0.816
Neonatal hypoglycemia	8 (1.5)	0	4 (3.6)	0.448	0.136
Neonatal hyperbilirubinemia	28 (5.3)	1 (2.6)	7 (6.3)	0.466	0.673
Neonatal admission	84 (15.8)	5 (13.2)	27 (24.1)	0.67	0.035
Perinatal death	0	0	0	–	–
Composite adverse outcome	82 (15.4)	6 (15.3)	28 (25)	0.987	0.014

GA, gestational age; SGA, small for GA, gestational age; FGR, fetal growth restriction. [1] Term FGR by GA-adjusted standards versus SGA. [2] Term FGR by both standards versus SGA.

have been conceived as unique and applied broadly to the whole population. In our multicenter randomized study (Ratio37) [12], we observed essential population differences in terms of normality ranges of Doppler values that could not be attributed to methodological issues since quality audits fail to see differences between the study sites [18]. This study shows that several maternal and fetal characteristics influence the umbilical and cerebral Doppler. This may partly explain the large differences that exist between the published normality ranges [8].

As we found in applying the fully adjusted Doppler standards to our cohort of SGA fetuses, adjusting by maternal and fetal characteristics allowed to reclassify a fraction of fetuses as (constitutional) SGA, which would otherwise have been considered growth restricted. This could have a relevant impact on both the number of inductions and elective C-sections since most guidelines recommend different management for SGA and FGR [21, 22]. Indeed, there is observational evidence [23] that selective induction of those SGA babies meeting criteria of FGR and more expectant management of constitutionally assumed SGA babies results in lower caesarean sections and improved neonatal outcomes as compared to systematic induction. We have previously shown that expectant management with close monitoring of SGA beyond 37 weeks results in perinatal outcomes comparable to those of normally grown babies [16].

Among all the maternal and fetal factors found to significantly influence Doppler measurements, maternal height stands out as one of the most determining. The mechanisms that reside under this finding are uncertain. In 2018, a study by Vinayagam et al. [24] assessed maternal hemodynamics in normal gestations and found an association between maternal height and a reduction in peripheral vascular resistances that could explain the decrease in umbilical PI in fetuses of tall mothers. Another study by a Norwegian group found lower rates of preeclampsia in tall women [25]. Regarding the other maternal characteristics, a study by Nicolaides et al. [7] observed that nulliparity was associated with an increased UA PI and reduced CPR. Our data show consistent results despite the fact that both populations are substantially different in many baseline and clinical characteristics. However, regarding maternal age, their study showed an association with a reduced UA PI and increased CPR, meanwhile our work found the opposite association. Finally, in female fetuses, higher UA PI has been previously reported [26]. Pregnant women carrying male fetuses are reported to have higher angiotensin 1–7 levels in the second trimester [27], which is a potent vasodilator that may explain these differences.

Our study's main strength is the large number of patients and participating centers, which confers external validity and power. The Doppler measurements have passed quality audits, enhancing internal validity. We also acknowledge some weaknesses in our study. First, being a retrospective analysis of the testing cohort, we cannot exclude a treatment paradox by which the large proportion of inductions (45%) in our group of FGR only by GA-adjusted standards can account for the good perinatal outcomes we observed in this group. However, in the group of FGR by both standards, the induction rate was even higher (56%) but the perinatal outcomes significantly poorer. Second, we do not have information on the uterine Doppler, which is also a Doppler parameter that has been proposed to define FGR as a reflection of the placental functioning from the maternal side [28]. Likewise, we do not have information on the placental findings to compare our study groups. Finally, it was not our aim to evaluate the effect of adjusted Doppler standards when used in the general population: our findings could not be directly translated into this clinical scenario. To conclude, our finding lays the groundwork for further exploring the effect of maternal and fetal physiological characteristics on fetal Doppler parameters and evaluating the clinical impact of using adjusted Doppler standards in the diagnosis and management of fetal growth near term.

Statement of Ethics

Written informed consent was obtained from all the patients for publication of this work. The study was approved by the Hospital Clinic Ethics Committee (RCTV01ABRIL). The Ratio37 study is registered with the next trial registration number NCT02907242.

Conflict of Interest Statement

Prof. Gratacos is the Editor in Chief, and Dr. M.C. Para-Cordero is an Editorial Board Member of *Fetal Diagnosis and Therapy*. Francesc Figueras is an AE of FDT. The other authors have no conflicts of interest to declare.

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Author Contributions

M.R.C. is the project monitor and contributed to the study planning and report and analysis of the data. A.R.V.S., M.L., L.H., A.K., J.M., L.K., J.V., E.F.P., C.R.G., M.P.C., P.S., E.Z., and M.C.L. contributed with their data on their respective sites. E.G. contributed to reviewing the article. F.F. is the general coordinator of the Ratio37 study and the PI of the project.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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