Do differences in diagnostic criteria for late fetal growth restriction matter?

TRUFFLE-2 Feasibility Study Authors; Mylrea-Foley, Bronacha; Napolitano, Raffaele; Gordijn, Sanne; Wolf, Hans; Lees, Christoph C.; Stampalija, Tamara

Published in:
American Journal of Obstetrics and Gynecology MFM

DOI:
10.1016/j.ajogmf.2023.101117

Publication date:
2023

Do differences in diagnostic criteria for late fetal growth restriction matter?

Bronacha Mylrea-Foley, MD; Raffaele Napolitano, MD, PhD; Sanne Gordijn, MD, PhD; Hans Wolf, MD; Christoph C. Lees, MD; Tamara Stampalija, MD, PhD; On behalf of TRUFFLE-2 Feasibility Study Authors

BACKGROUND: Criteria for diagnosis of fetal growth restriction differ widely according to national and international guidelines, and further heterogeneity arises from the use of different biometric and Doppler reference charts, making the diagnosis of fetal growth restriction highly variable.

OBJECTIVE: This study aimed to compare fetal growth restriction definitions between Delphi consensus and Society for Maternal-Fetal Medicine definitions, using different standards/charts for fetal biometry and different reference ranges for Doppler velocimetry parameters.

STUDY DESIGN: From the TRUFFLE 2 feasibility study (856 women with singleton pregnancy at 32^{+0} to 36^{+6} weeks of gestation and at risk of fetal growth restriction), we selected 564 women with available mid-pregnancy biometry. For the comparison, we used standards/charts for estimated fetal weight and abdominal circumference from Hadlock, INTERGROWTH-21st, and GROW and Chitty. Percentiles for umbilical artery pulsatility index and its ratios with middle cerebral artery pulsatility index were calculated using Arduini and Ebbing reference charts. Sensitivity and specificity for low birthweight and adverse perinatal outcome were evaluated.

RESULTS: Different combinations of definitions and reference charts identified substantially different proportions of fetuses within our population as having fetal growth restriction, varying from 38% (with Delphi consensus definition, INTERGROWTH-21st biometric standards, and Arduini Doppler reference ranges) to 93% (with Society for Maternal-Fetal Medicine definition and Hadlock biometric standards). None of the different combinations tested appeared effective, with relative risk for birthweight <10th percentile between 1.4 and 2.1. Birthweight <10th percentile was observed most frequently when selection was made with the GROW/Chitty charts, slightly less with the Hadlock standard, and least frequently with the INTERGROWTH-21st standard. Using the Ebbing Doppler reference ranges resulted in a far higher proportion identified as having fetal growth restriction compared with the Arduini Doppler reference ranges, whereas Delphi consensus definition with Ebbing Doppler reference ranges produced similar results to those of the Society for Maternal-Fetal Medicine definition. Application of Delphi consensus definition with Arduini Doppler reference ranges was significantly associated with adverse perinatal outcome, with any biometric standards/charts. The Society for Maternal-Fetal Medicine definition could not accurately detect adverse perinatal outcome irrespective of estimated fetal weight standard/chart used.

CONCLUSION: Different combinations of fetal growth restriction definitions, biometry standards/charts, and Doppler reference ranges identify different proportions of fetuses with fetal growth restriction. The difference in adverse perinatal outcome may be modest, but can have a significant impact in terms of rate of intervention.

Key words: brain sparing, cerebral redistribution, cerebroplacental ratio, chart, Doppler, fetal growth restriction, intrauterine growth restriction, middle cerebral artery, reference, small for gestational age, standard, umbilical-cerebral ratio

Introduction

Fetal growth restriction (FGR), whereby a fetus fails to reach its growth potential, is a common pregnancy complication. Timely diagnosis is crucial because of its association with perinatal risks including stillbirth, neonatal morbidity, and longer-term neurodevelopmental delay.[1,2] Indeed, the risk of stillbirth is greater if FGR is not recognized antenatally.[3] Women with FGR therefore require close monitoring of the fetal condition and early delivery if signs of fetal compromise are recognized. Certain challenges regarding the diagnosis of FGR are widely acknowledged, including the assumption that FGR is always related to small fetal size and the difficulty in distinguishing healthy, constitutionally small for gestational age (SGA) fetuses from those with FGR requiring intervention.[4–7]

The criteria for diagnosis of FGR differ widely according to national and international guidelines. Several define FGR simply by size: abdominal circumference (AC) or estimated fetal weight (EFW) <10th percentile.[8,9] The consensus definitions proposed by Gordijn et al[10] following a Delphi process also take into account Doppler changes and fetal growth velocity. These definitions, for early and late FGR, are adopted by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)[5] and by the International Federation of Gynecology and Obstetrics (FIGO) guidelines on FGR.[11] Moving away from a definition based on fetal size, the Delphi consensus definition for late FGR (after 32 weeks of gestation) requires EFW or AC <3rd percentile, or EFW/AC <10th percentile and/or a drop in AC or EFW of >50 percentile points after mid-pregnancy ultrasound, in combination with an umbilical artery pulsatility index (PI) >95th percentile or cerebroplacental ratio (CPR) <5th percentile. The Delphi consensus definition did not specify which reference ranges should be used for fetal biometry or Doppler values. However, the selection of the specific biometric and Doppler reference ranges has an impact on the prevalence of FGR and thus on clinical management,[12,13] and significant

Cite this article as: Mylrea-Foley B, Napolitano R, Gordijn S, et al. Do differences in diagnostic criteria for late fetal growth restriction matter? Am J Obstet Gynecol MFM 2023;5:101117.

2589-9333/$36.00

http://dx.doi.org/10.1016/j.ajogmf.2023.101117

AJOG MFM at a Glance

Why was this study conducted?

Detection of compromised fetuses is essential for reduction of perinatal morbidity and mortality associated with growth restriction. However, nonspecific definitions expose many constitutionally small fetuses to unnecessary interventions and complications associated with late preterm delivery.

Key findings

Different combinations of definitions and reference charts identified notably different proportions of fetuses as having fetal growth restriction (FGR) within our study population (varying from 38% to 93%). None of the combinations tested appeared effective, with relative risk for birthweight <10th percentile between 1.4 and 2.1 and relative risk for adverse perinatal outcome between 0.9 and 2.1, both with particularly poor specificity.

What does this add to what is known?

This study provided a comparison encompassing FGR definitions, biometric standards/charts, and Doppler reference ranges, and thus an accurate representation of clinical practice in relation to published clinical guidance. We cannot determine from these data the optimal combination of diagnostic criteria and reference ranges. Instead, there is a choice between more strict and more permissive diagnostic criteria, which shifts sensitivity and specificity in generally opposite directions.

heterogeneity has been reported for some countries.[14] The FGR definition by the Society for Maternal-Fetal Medicine (SMFM) guideline[9] is based on fetal size and expresses a preference for the Hadlock EFW standard.[15]

The objective of this secondary analysis of data from the TRUFFLE 2 feasibility study[16] is to describe and compare the ability of both the Delphi consensus[10] and SMFM[9] definitions to select women with late preterm FGR with the highest risk for perinatal adverse outcome, applying a range of widely used reference charts for fetal biometry and fetal arterial Doppler velocimetry.

Materials and Methods

The study population has been described previously.[16] In brief, we included women with a singleton pregnancy from 32^{+0} to 36^{+6} weeks of gestation with a fetus considered at risk of FGR, defined as EFW and/or AC <10th percentile, and/or abnormal fetal arterial Doppler, and/or a fall in AC growth velocity of >40 percentile points from the mid-pregnancy scan. Regarding study selection reference ranges, EFW, AC, and Doppler parameters were based on local charts. Similarly, the definition of birthweight <10th percentile was based on local charts. To be eligible, the fetus had to have positive umbilical artery end-diastolic flow and a normal computerized cardiotocograph (cCTG) with short-term variation of the fetal heart rate >3.0 ms using Dawes−Redman cCTG analysis. Gestational age was calculated from certain menstrual age and/or ultrasound assessment before 22 weeks of gestation. Women were ineligible for inclusion if there was known, planned, or impending delivery based on fetal condition, maternal obstetrical complications, uterine contractions, or rupture of membranes, or if the fetus had a known or suspected structural or chromosomal abnormality. From the study population, only women with a mid-pregnancy AC measurement were selected. EFW at mid-pregnancy was not collected in the database.

The primary outcome was a composite of abnormal condition at birth or major neonatal morbidity. Abnormal condition at birth was defined as at least 1 of the following: Apgar score <7 at 5 minutes, umbilical artery pH <7.0 or umbilical vein pH <7.1, resuscitation with intubation, chest compressions or resuscitation medications, or stillbirth. Major neonatal morbidity until first discharge home was defined as at least 1 of the following: neurologic abnormality (intracerebral hemorrhage grade 3 or 4, periventricular leukomalacia grade 2 or 3, encephalopathy, or seizures necessitating antiepileptic drug treatment); cardiovascular abnormality (hypotensive treatment, ductus arteriosus treatment, or disseminated coagulopathy); respiratory morbidity (respiratory support for >1 week, mechanical ventilation, meconium aspiration, or persistent pulmonary hypertension); or sepsis (clinical sepsis with positive blood culture, necrotizing enterocolitis [Bell's stage ≥2], or meningitis).

For the calculations, 2 different definitions for FGR were compared:

1. Delphi consensus definition for late FGR[10]: EFW or AC <3rd percentile, or combination of EFW and/or AC <10th percentile and/or percentile drop of >50 centiles, and an umbilical artery PI or umbilicocerebral ratio (UCR) >95th percentile (or CPR <5th percentile);
2. SMFM definition for FGR[9]: EFW or AC <10th percentile.

The value of EFW and percentiles for EFW and AC were calculated using:

1. Hadlock: EFW was calculated with the Hadlock EFW algorithm,[17] and the percentiles by the Hadlock EFW standard[15] and the Hadlock AC standard[18];
2. INTERGROWTH-21st: EFW was calculated using the INTERGROWTH-21st EFW calculator,[19] and the percentiles by the INTERGROWTH-21st EFW standard[19] and the INTERGROWTH-21st AC standard[20];
3. GROW/Chitty: EFW was calculated using the Hadlock EFW algorithm,[17] and the percentiles by the GROW chart, version 8.0.4.[21] These percentiles were adjusted for maternal height, weight, and parity, and fetal sex. Ethnicity was not recorded

TABLE 1
Characteristics of the study population (n=564)

Characteristics	All
N	564
Age	32 (28–36)
BMI	22.2 (20.2–25.9)
Nullipara	337 (60%)
Preeclampsia	52 (9%)
Hypertensive complication (GH or PE)	83 (15%)
20-wk scan	
Gestational age (wk)	20.1 (19.6–20.7)
AC (mm)	147 (138–155)
Inclusion	
Gestational age (wk)	34.0 (32.9–35.6)
Study inclusion <p10	519 (92%)
50% AC drop	46 (8%)
Doppler	70 (12%)
AC (mm)	272 (259–285)
AC <p10 (Chitty)	354 (63%)
AC <p10 (Hadlock)	508 (90%)
AC <p10 (INTERGROWTH-21st)	359 (64%)
AC drop >50% (Chitty)	135 (24%)
AC drop >50% (Hadlock)	91 (16%)
AC drop >50% (INTERGROWTH-21st)	158 (28%)
EFW (g) calculated (Hadlock)	1894 (1616–2166)
EFW (g) calculated (INTERGROWTH-21st)	1712 (1488–1948)
EFW <p10 (Hadlock)	455 (81%)
EFW <p10 (INTERGROWTH-21st)	425 (75%)
EFW <p10 (GROW)	370 (66%)
Umbilical artery PI	1.01 (0.87–1.15)
Umbilical artery PI ≥p95 (Arduini)	24 (4%)
Umbilical artery PI ≥p95 (Ebbing)	413 (73%)
UCR	0.57 (0.47–0.70)
UCR ≥p95 (Arduini)	27 (5%)
CPR <p5 (Ebbing)	216 (38%)
Delivery	
Cesarean delivery before labor	133 (23%)
Fetal indication	40 (30%)
Cesarean delivery in labor	81 (14%)
Fetal indication	43 (53%)
Gestational age	38.0 (36.9–39.1)
Birthweight (g)	2450 (2113–2753)

(continued)

in the database, and was therefore fixed at "Western Europe". AC percentiles were calculated using the Chitty AC chart.[22]

Percentiles for umbilical artery PI and UCR/CPR were calculated using:

1. Arduini and Rizzo[23] UCR reference ranges;
2. Ebbing et al[24] CPR reference ranges.

Arduini UCR values were converted to CPR using the inverse (1/UCR) in relation to gestational age.

Biometry and Doppler values at inclusion were used for assessment. Abnormal vs normal selection by different criteria for FGR were compared by perinatal data: maternal parity, body mass index, gestational age at delivery, birthweight <10th percentile of the corresponding EFW standards/charts (either Hadlock, INTERGROWTH-21st, or GROW), cesarean delivery indicated by fetal condition, neonatal sex, and composite adverse perinatal outcome.

Statistical methods

Data are presented as number with percentage or median with interquartile range (IQR). Groups were compared by median test, Fisher exact test, or chi-square test, as appropriate. Statistical significance was determined by 2-sided P value <.05. Calculations were made with IBM SPSS Statistics software, Version 27.0 (IBM Corp, Armonk, NY).

Ethical approval

The study was observational, and practice (monitoring, delivery, steroid administration) was based on local guidelines. Data were recorded and anonymized after outcomes were obtained. In 6 countries (19 centers), ethical approval was obtained, and participants provided informed signed consent. In the remaining 5 countries, formal ethical approval was not required.

Results

The characteristics of the study population are represented in Table 1. Of the TRUFFLE 2 feasibility study population

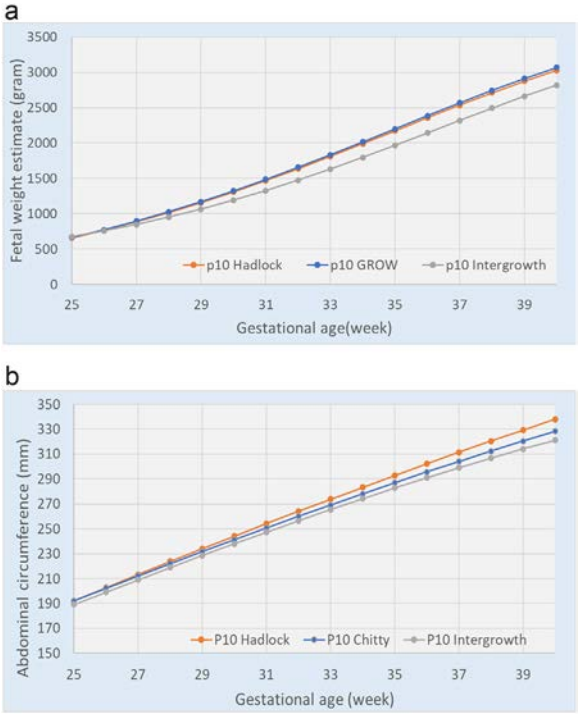
TABLE 1
Characteristics of the study population (n=564) *(continued)*

Characteristics	All
Birthweight <p10 (Hadlock)	414 (73%)
Birthweight <p10 (INTERGROWTH-21st)	314 (56%)
Birthweight <p10 (GROW)	424 (75%)
Male sex	252 (45%)
Outcomes	
Composite adverse infant outcome	64 (11%)
Adverse condition at birth	19 (3%)
Major neonatal morbidity	53 (9%)

AC, abdominal circumference; *BMI*, body mass index; *CPR*, cerebroplacental ratio; *EFW*, estimated fetal weight; *GH*, gestational hypertension; *p5*, fifth percentile; *p10*, 10th percentile; *p95*, 95th percentile; *PE*, preeclampsia; *PI*, pulsatility index; *UCR*, umbilicocerebral ratio.

Mylrea-Foley. Differences in late fetal growth restriction diagnosis. Am J Obstet Gynecol MFM 2023.

FIGURE 1
Comparison of different biometry charts



A, The 10th percentile of EFW using the GROW, Hadlock, and INTERGROWTH-21st EFW standards/charts. Calculated for a West-European mother with a height of 1.70 m and a weight of 72 kg, and a male fetus. For a mother with lower height and weight, and for a female fetus, the line will be lower; for a larger mother, the line will be higher. **B**, The 10th percentile of abdominal circumference (AC) using Hadlock, Chitty, and INTERGROWTH-21st AC standards/charts.

EFW, estimated fetal weight; *p10*, 10th percentile.

Mylrea-Foley. Differences in late fetal growth restriction diagnosis. Am J Obstet Gynecol MFM 2023.

of 856 women, 564 (66%) had a mid-pregnancy AC measurement recorded, allowing for calculation of an AC percentile drop and inclusion in this analysis.

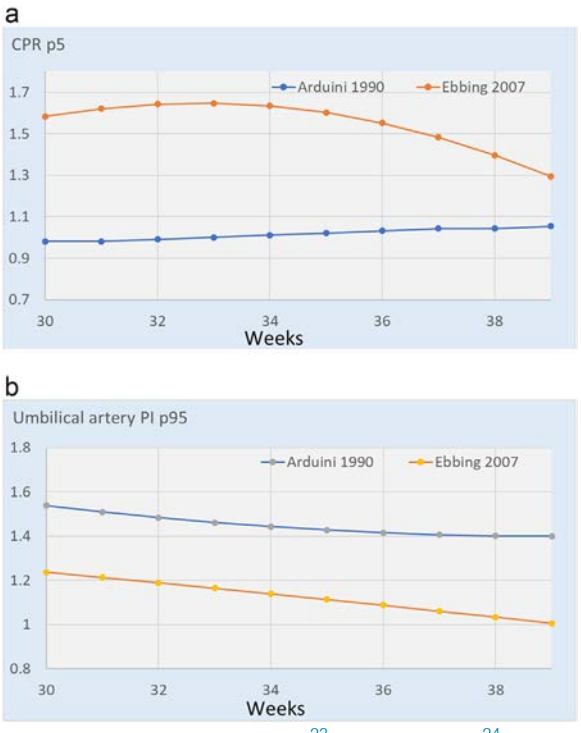
Calculation of EFW using the Hadlock algorithm resulted in a significantly greater estimated weight compared with the INTERGROWTH-21st calculator (median proportional difference, 7%; IQR, 4−10; $P<.001$).

Figure 1, A and B compares the 10th percentile of EFW and AC between the 3 selected standards/charts. Hadlock and GROW EFW 10th percentiles are similar, whereas the INTERGROWTH-21st 10th percentile is approximately 10% lower. The Hadlock EFW standard selected 81% of the fetuses as <10th percentile, as opposed to 66% using the GROW chart. Using the INTERGROWTH-21st EFW calculator, which results in approximately 10% lower weight compared with the Hadlock EFW algorithm, the proportion <10th percentile was 76%. The AC 10th percentile by Hadlock is approximately 10% higher than that of INTERGROWTH-21st, with Chitty in between. The percentage of women at inclusion with an AC <10th percentile was higher using the Hadlock AC standard (90%) than Chitty or INTERGROWTH-21st (63% and 64%, respectively).

The difference between Arduini and Ebbing Doppler reference ranges for CPR 5th percentile and umbilical artery PI 95th percentile values was large (Figure 2, A and B): between 30 and 38 weeks of gestation, it ranges between approximately 50% and 30% for CPR, and approximately 30% for umbilical artery PI. Whereas only 5% of the population had a UCR >95th percentile according to the Arduini reference ranges, 38% had a CPR <5th percentile according to Ebbing reference ranges. The difference for umbilical artery PI ≥95th percentile was even larger: 4% for Arduini and 73% for Ebbing reference ranges.

The percentage of women in our cohort identified as having FGR on the basis of different diagnostic criteria, biometric standards/charts, and Doppler reference ranges is shown in Figure 3.

FIGURE 2
Comparison of Arduini and Ebbing Doppler charts



A, The line plot of the CPR p5 by Arduini and Rizzo[23] and Ebbing et al[24] reference ranges. Gestational age window from 30 to 39 weeks is represented (Arduini p95 converted to CPR by 1/umbilicocerebral ratio). **B**, The line plot of the umbilical artery PI p95 by Arduini and Rizzo[23] and Ebbing et al[24] reference ranges. Gestational age window from 30 to 39 weeks is represented.

CPR, cerebroplacental ratio; *p5*, fifth percentile; *p95*, 95th percentile; *PI*, pulsatility index.

Mylrea-Foley. Differences in late fetal growth restriction diagnosis. Am J Obstet Gynecol MFM 2023.

This varied from 38% with Delphi consensus definition, INTERGROWTH-21st biometric standards, and Arduini Doppler reference ranges, to 93% with SMFM definition and Hadlock biometric standards. The data are further specified in Table 2. Within all definitions, the Hadlock EFW standard resulted in the highest percentage of the study population identified as having FGR, and INTERGROWTH-21st and GROW/Chitty resulted in similar percentages. Using Ebbing Doppler reference ranges resulted in a far higher selection of FGR than with Arduini Doppler reference ranges, whereas Delphi consensus definition with Ebbing Doppler reference ranges produced similar results to those found with the SMFM definition.

A drop in AC did not contribute to the identification of FGR using the Delphi consensus definition with Arduini Doppler reference ranges, whereas with Ebbing Doppler reference ranges, identification depended on the EFW standard/chart used, and was minimal with Hadlock (1%), more frequent with GROW/Chitty (4%), and most frequent with INTERGROWTH-21st (8%).

Figure 4 shows the percentage of our study population identified as having FGR by different criteria, who gave birth to an infant with a birthweight <10th percentile. The data are further specified in Table 2. Birthweight <10th percentile was observed most frequently when selection was made with the GROW/Chitty charts, slightly less with the Hadlock standard, and least frequently with the INTERGROWTH-21st standard. As shown in Figure 5, all combinations resulted in a statistically significant selection of pregnancies resulting in a birthweight <10th percentile; however, the relative risks (RRs) were low (1.4 to 2.1). Any combination with Hadlock standards selected the highest absolute number of FGR and birthweight <10th percentile (Table 2). By applying Arduini Doppler reference ranges and Hadlock standards, 17% of the infants with a birthweight <10th percentile in our study population would have been missed. With INTERGROWTH-21st or GROW/Chitty in combination with Arduini, approximately 50% would have been missed.

Adverse perinatal outcome occurred in 11% of the population (Table 1). Figure 6 shows the percentage of the women with adverse perinatal outcome in the study population who were selected by the different criteria. The data are further specified in Table 3. Applying Delphi consensus definition with Arduini Doppler reference ranges was significantly associated with adverse perinatal outcome, with any biometric standards/charts (relative risk [RR], 1.9−2.1). As shown in Figure 7, the SMFM definition could not accurately detect adverse perinatal outcome irrespective of EFW standard/chart used (RR, 0.9−1.4).

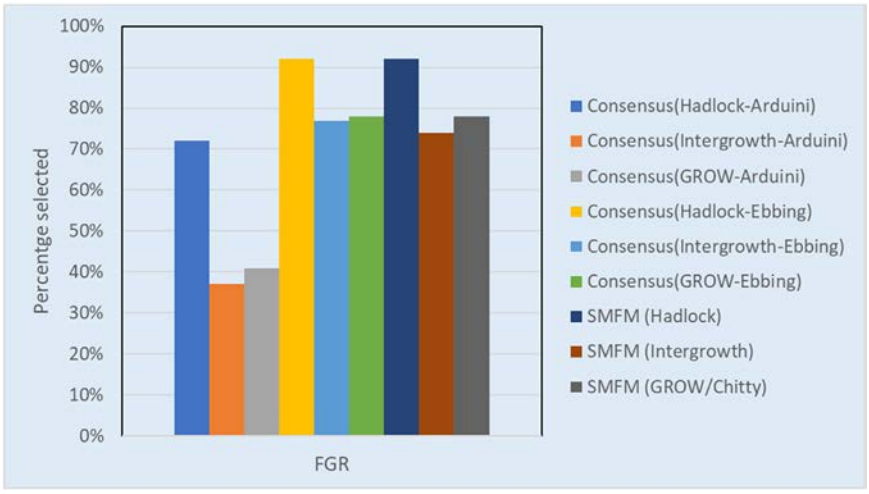
Comment

Principal findings

In this population of women selected as having fetuses at risk of growth restriction, there was remarkable variation in FGR identification according to the biometric and Doppler reference charts and the definitions used. This is notwithstanding the fact that the different defining criteria for FGR have been designed by consensus of experienced obstetricians or endorsed by professional organizations, and all reference ranges have been carefully developed in high-quality studies. None of the different combinations tested appeared accurate, with RR for birthweight <10th percentile between 1.4 and 2.1 and RR for adverse perinatal outcome between 0.9 and 2.1, both with poor specificity.

Given that women were selected on the basis of EFW, AC <10th percentile, or AC growth slowdown, with most

FIGURE 3
Identification of FGR using different criteria



FGR, fetal growth restriction; *SMFM*, Society for Maternal-Fetal Medicine.

Mylrea-Foley. Differences in late fetal growth restriction diagnosis. Am J Obstet Gynecol MFM 2023.

having an AC <10th percentile, it stands to reason that the SMFM definition using AC/EFW <10th percentile had the highest sensitivity for birthweight <10th percentile. Naturally, when a larger percentage of women is identified as having FGR, the percentage of missed low birthweight decreases. We could not determine the proportion of infants with FGR among those with a birthweight <10th percentile, and therefore we used adverse perinatal outcome as an indicator for true FGR. We observed similar findings with adverse perinatal outcome as with low birthweight. Combinations of criteria that identified a larger percentage of our population as having FGR resulted in fewer missed cases but a lower incidence of adverse outcome.

For this study, we selected the 3 most commonly used EFW standards/charts currently available. We did not document ethnicity in the database, and therefore we set ethnicity as "Western European" for the GROW percentile calculation. We did not use the World Health Organization (WHO) fetal weight chart,[25] which uses the Hadlock formula with an adjustment for local average birthweight at 40 weeks. We assumed that average birthweight in Western Europe and United States is similar and that therefore WHO and Hadlock standards would be similar.

TABLE 2
Numbers of women selected with different criteria for FGR, with numbers and rates of birthweight <10th percentile, and relative risks and 95% confidence intervals

FGR definition	Criteria abnormal		Criteria normal		Sensitivity/ specificity	Only selected as abnormal with AC 50% change
	N (% of total)	Birthweight <p10	N (% of total)	Birthweight <p10		
Delphi consensus definition with Arduini Doppler reference ranges						
Hadlock	431 (76%)	342 (79%)[a]	133 (24%)	72 (54%)	82%/41%	0/431 (0%)
INTERGROWTH-21st	213 (38%)	154 (72%)[a]	351 (62%)	160 (46%)	49%/76%	0/35 (0%)
GROW/Chitty	242 (43%)	219 (91%)[a]	322 (57%)	205 (64%)	52%/84%	0/242 (0%)
Delphi consensus definition with Ebbing Doppler reference ranges						
Hadlock	525 (93%)	400 (76%)[a]	39 (7%)	14 (36%)	97%/17%	6/525 (1%)
INTERGROWTH-21st	464 (82%)	280 (60%)[a]	100 (18%)	34 (34%)	89%/26%	35/464 (8%)
GROW/Chitty	455 (81%)	370 (81%)[a]	109 (19%)	54 (50%)	87%/39%	17/455 (4%)
SMFM definition						
Hadlock	526 (93%)	400 (76%)[a]	38 (7%)	14 (37%)	97%/16%	
INTERGROWTH-21st	439 (78%)	273 (62%)[a]	125 (22%)	41 (33%)	87%/34%	
GROW/Chitty	449 (80%)	368 (82%)[a]	115 (20%)	56 (49%)	87%/42%	

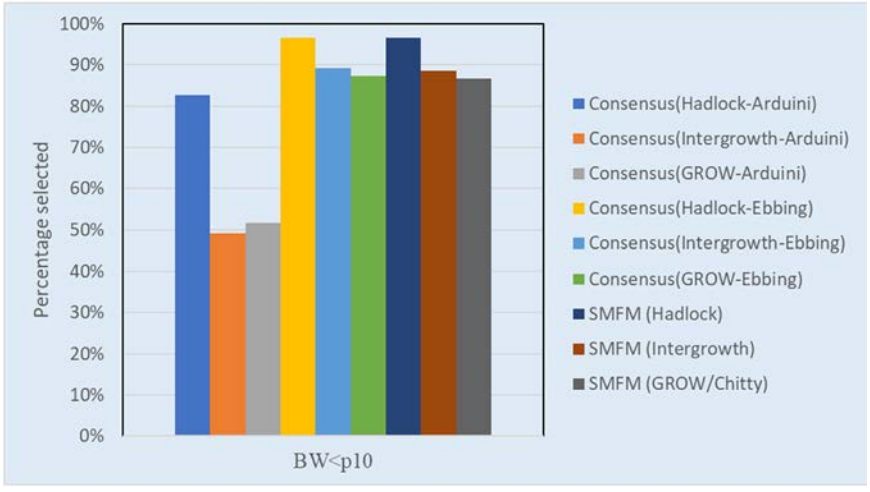
Calculations for selection and birthweight were performed according to the reference charts specified in the left column.

AC, abdominal circumference; *FGR*, fetal growth restriction; *p10*, 10th percentile; *SMFM*, Society for Maternal-Fetal Medicine.

[a] Comparison of selected women with unselected women; $P<.05$ (Fisher exact test).

Mylrea-Foley. Differences in late fetal growth restriction diagnosis. Am J Obstet Gynecol MFM 2023.

FIGURE 4
Identification of FGR within infants of birthweight <10th percentile using different criteria



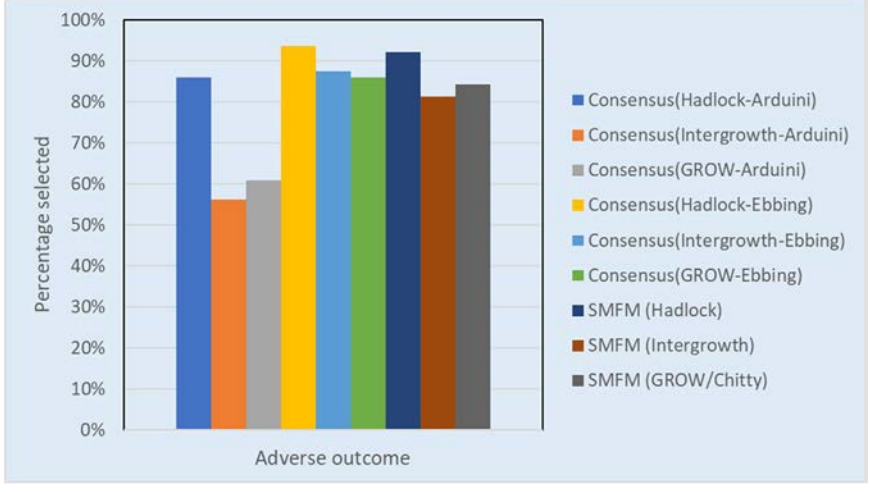
BW percentiles were calculated by the specific BW chart of the subgroup.

BW, birthweight; *FGR*, fetal growth restriction; *p10*, 10th percentile.

Mylrea-Foley. Differences in late fetal growth restriction diagnosis. Am J Obstet Gynecol MFM 2023.

Reference ranges for EFW are lower in the INTERGROWTH-21st standard, which also recruited women from India, China, and South America.[20,26] Although only women with optimal socioeconomic and health status were included in this study, this might be insufficient to fully adjust for regional differences. For Doppler references, we chose the Arduini and Ebbing reference ranges to represent extremes because in a recent comparison these had the lowest and highest values,[13] and both were studies of high quality.[27]

FIGURE 5
Identification of FGR within infants with adverse outcome using different criteria



FGR, fetal growth restriction.

Mylrea-Foley. Differences in late fetal growth restriction diagnosis. Am J Obstet Gynecol MFM 2023.

Results in the context of what is known

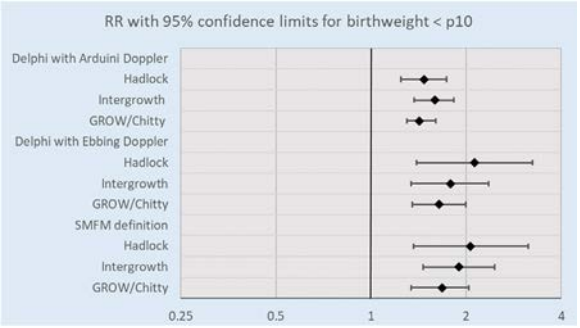
Previous studies have separately assessed the ability of different biometric charts[28–31] and definitions[32,33] to predict low birthweight and adverse outcome, similarly finding varying levels of sensitivity and poor predictive performance overall. No studies to date have assessed how the combined choice of definitions, biometric standards/charts, and Doppler reference ranges can affect the detection of FGR and prediction of low birthweight and adverse perinatal outcome.

Clinical implications

As sensitivity for FGR increases, specificity generally falls. Overall, false-negatives were lowest with Delphi consensus definition using Ebbing Doppler reference ranges or SMFM definition in combination with Hadlock EFW standard (3%). False-positives cannot be assessed with the current study population because it was selected on the basis of suspicion of FGR. The highest RR (approximately 2) for adverse perinatal outcome was found for fetuses identified as having FGR by Delphi consensus definition with INTERGROWTH-21st EFW standard and Arduini Doppler reference range This is in contrast to the lower RR for adverse perinatal outcome found when using the SMFM definition irrespective of EFW standard.

Similar to the effect of false vs true diagnosis of FGR on adverse perinatal outcome, the effect of necessary vs unnecessary interventions should be considered. A recent simulation analysis of a cohort of SGA fetuses showed that use of different Doppler reference ranges can significantly alter clinical management.[12] These differences between criteria potentially affect interventions within the population of SGA babies. These differences between criteria affect the clinical workload and the rate of intervention within the population. It is at the discretion of any given

FIGURE 6
Forrest plot of birthweight <10th percentile using different FGR criteria



FGR, fetal growth restriction; *p10*, 10th percentile; *RR*, relative risk; *SMFM*, Society for Maternal-Fetal Medicine.
Mylrea-Foley. Differences in late fetal growth restriction diagnosis. Am J Obstet Gynecol MFM 2023.

society to choose which reference ranges they consider appropriate for their population.

Research implications

We cannot determine from these data the optimal combination of diagnostic criteria and reference ranges. Given the lack of precision of biometry and Doppler for the prediction of adverse perinatal outcome, there are probably no perfect diagnostic criteria. Instead, there is a choice between more strict and more permissive diagnostic criteria, which shifts sensitivity and specificity in generally opposite directions. For research purposes, the Delphi consensus definition with Hadlock EFW standards and Arduini Doppler reference ranges is the most selective, increasing the chance that those selected represent "true" FGR. For clinical purposes, more permissive diagnostic criteria (eg, SMFM definition with the Hadlock EFW standard) might be preferable to minimize missed cases.

Strengths and limitations

This study provided a comparison encompassing FGR definitions, biometric standards/charts, and Doppler reference ranges, and thus an accurate representation of clinical practice in relation to published clinical guidance.[9,10] The strengths of this study include the large, preselected population, with high outcome ascertainment, in a study involving

TABLE 3
Numbers of women selected with different criteria for FGR, with the numbers and rates of abnormal primary end point, sensitivity/specificity, and relative risks and 95% confidence intervals

	Criteria abnormal		Criteria normal		
FGR definition	N (% of total)	Primary study end point abnormal	N (% of total)	Primary study end point abnormal	Sensitivity/ specificity
Delphi consensus definition with Arduini Doppler reference ranges					
Hadlock	431 (76%)	55 (13%)[a]	133 (24%)[a]	9 (7%)	86%/25%
INTERGROWTH-21st	213 (38%)	36 (17%)[a]	351 (62%)	28 (8%)	56%/65%
GROW/Chitty	242 (43%)	39 (16%)[a]	322 (57%)	25 (8%)	61%/59%
Delphi consensus definition with Ebbing Doppler reference ranges					
Hadlock	525 (93%)	60 (11%)	39 (7%)	4 (10%)	94%/7%
INTERGROWTH-21st	464 (82%)	56 (12%)	100 (18%)	8 (8%)	88%/18%
GROW/Chitty	455 (81%)	55 (12%)	109 (19%)	9 (8%)	86%/20%
SMFM definition					
Hadlock	526 (93%)	59 (11%)	38 (7%)	5 (13%)	92%/7%
INTERGROWTH-21st	439 (78%)	52 (12%)	125 (22%)	12 (10%)	81%/23%
GROW/Chitty	449 (80%)	54 (12%)	115 (20%)	10 (9%)	84%/21%

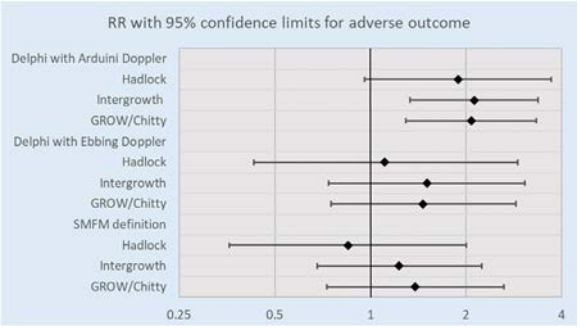
Calculations for selection were performed according to the reference charts specified in the left column.

FGR, fetal growth restriction; *SMFM*, Society for Maternal-Fetal Medicine.

[a] Comparison of selected women with unselected women; $P<.05$ (Fisher exact test).

Mylrea-Foley. Differences in late fetal growth restriction diagnosis. Am J Obstet Gynecol MFM 2023.

FIGURE 7
Forrest plot of adverse composite outcome using different FGR criteria



FGR, fetal growth restriction; *RR*, relative risk; *SMFM*, Society for Maternal-Fetal Medicine.

Mylrea-Foley. Differences in late fetal growth restriction diagnosis. Am J Obstet Gynecol MFM 2023.

ultrasound and Doppler experts. Another advantage was the ability to compare adverse perinatal outcome for a population selected by local standards as being at risk of FGR with internationally proposed standards for FGR. It was not the aim of our study to explore different birthweight charts because this would inevitably introduce methodological bias in the comparison of prenatal and postnatal charts from the same group.

The main limitation of this study is that we do not report on an unselected population, instead testing how diagnosis of FGR would have differed with different diagnostic criteria and reference ranges within a population of women at risk of FGR. Another difficulty specific to FGR studies is that adverse perinatal outcomes recorded can either be the result of the condition (FGR and hypoxemia) or the intervention (early delivery and relative prematurity).[34] Another weakness of this study is that investigators who participated in the study were obstetricians/fetal medicine experts and the parameters studied were also used in clinical management. The former might have led to more frequent surveillance than expected, and the latter might represent a source of intervention bias variably prominent between diagnostic criteria. However, this type of bias is typical for all observational studies and avoidable only by a randomized controlled trial.

Conclusions

Different combinations of FGR definitions, biometry standards/charts, and Doppler reference ranges identify remarkably different proportions of fetuses with FGR. The differences in the sensitivity for adverse perinatal outcome may be modest, but can have a significant impact in terms of clinical workload and rates of intervention. ■

ACKNOWLEDGMENTS

We would like to acknowledge the TRUFFLE 2 Feasibility Study collaborating authors:

C. Brezinka, MD, Department of Obstetrics and Gynaecology, Medical University of Innsbruck, Innsbruck, Austria; D. Casagrandi, MD, University College London Hospitals NHS Foundation Trust, London, United Kingdom; A. Cerny, MD, Department of Obstetrics and Gynaecology, General University Hospital and First Faculty of Medicine, Charles University, Prague, Czech Republic; A. Dall'Asta, MD, Department of Obstetrics and Gynecology, University of Parma, Parma, Italy; R. Devlieger, MD, Department of Gynaecology and Obstetrics, Universitair Ziekenhuis Leuven, and Department of Regeneration and Development, Katholieke Universiteit Leuven, Leuven, Belgium; J. Duvekot, MD, Erasmus University Medical Centre, Rotterdam, The Netherlands; T. M. Eggebo, MD, St Olav's University Hospital, Trondheim, Norway; I. Fantasia, MD, Unit of Fetal Medicine and Prenatal Diagnosis, Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste, Italy; F. Ferrari, MD, Obstetrics and Gynecology, Polyclinic University Hospital of Modena, Modena, Italy; N. Fratelli, MD, Department of Obstetrics and Gynecology, L'Azienda Socio Sanitaria Territoriale (ASST) degli Spedali Civili di Brescia and University of Brescia, Brescia, Italy; M. Georg, MD, Helsinki University Central Hospital, Helsinki, Finland; T. Ghi, MD, Department of Obstetrics and Gynecology, University of Parma, Parma, Italy; O. Graupner, MD, Department of Obstetrics and Gynecology, Klinikum Rechts Der Isar, Technical University of Munich, Munich, Germany; P. Greimel, MD, Department of Obstetrics and Gynaecology, Medical University of Graz, Graz, Austria; C. Hofstaetter, MD, Department of Obstetrics and Gynecology, University Hospital of Bern, Bern, Switzerland; D. Lo Presti, MD, Division of Obstetrics and Gynaecology, Department of Surgery, Tor Vergata University of Rome, Policlinico Casilino Hospital, Rome, Italy; F. Macsali, MD, Department of Obstetrics and Gynecology, Haukeland University Hospital, Bergen, Norway; K. Marsal, MD,† Department of Obstetrics and Gynaecology, Lund University, Skåne University Hospital, Lund, Sweden; P. Martinelli, MD, Department of Neuroscience, Reproductive Sciences and Dentistry, University of Naples Federico II, Naples, Italy; E. Mullins, MD, Imperial College London, London, United Kingdom; E. Ostermayer, MD, Department of Obstetrics and Gynecology, Klinikum Rechts Der Isar, Technical University of Munich, Munich, Germany; A. Papageorghiou, MD, Fetal Medicine Unit, St George's University Hospitals NHS Foundation Trust and Molecular and Clinical Sciences Research Institute, St George's, University of London, London, United Kingdom; R. Peasley, Fetal Medicine Unit, University College London Hospitals NHS Foundation Trust, London, United Kingdom; A. Ramoni, MD, Department of Obstetrics and Gynaecology, Medical University of Innsbruck, Innsbruck, Austria; L. Sarno, MD, Department of Neuroscience, Reproductive Sciences and Dentistry, University of Naples Federico II, Naples, Italy; L. Seikku, MD, Helsinki University Central Hospital, Helsinki, Finland; S. Simeone, MD, Department of Health Sciences, University of Florence, and Department of Obstetrics and Gynecology, Careggi University Hospital, Florence, Italy; B. Thilaganathan, MD, Fetal Medicine Unit, St George's University Hospitals NHS Foundation Trust and Molecular and Clinical Sciences Research Institute, St George's, University of London, London, United Kingdom; G. Tiralongo, MD, Division of Obstetrics and Gynaecology, Department of Surgery, Tor Vergata University of Rome, Policlinico Casilino Hospital, Rome, Italy; A. Valcamonico, MD, Department of Obstetrics and Gynecology, ASST Spedali Civili di Brescia and University of Brescia, Brescia, Italy; C. Van Holsbeke, MD, Department of Obstetrics and Gynaecology, Ziekenhuis Oost-Limburg, Genk, Belgium; and

† Author Deceased.

A. Vietheer, MD, Department of Obstetrics and Gynecology, Haukeland University Hospital, Bergen, Norway.

References

1. Baschat AA. Planning management and delivery of the growth-restricted fetus. Best Pract Res Clin Obstet Gynaecol 2018;49:53–65.

2. Meher S, Hernandez-Andrade E, Basheer SN, Lees C. Impact of cerebral redistribution on neurodevelopmental outcome in small-for-gestational-age or growth-restricted babies: a systematic review. Ultrasound Obstet Gynecol 2015;46:398–404.

3. Gardosi J, Madurasinghe V, Williams M, Malik A, Francis A. Maternal and fetal risk factors for stillbirth: population based study. BMJ 2013;346:f108.

4. Stampalija T, Wolf H, Mylrea-Foley B, et al. Reduced fetal growth velocity and weight loss are associated with adverse perinatal outcome in fetuses at risk of growth restriction. Am J Obstet Gynecol 2023;228. 71.e1–10.

5. Lees CC, Stampalija T, Baschat AA, et al. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. Ultrasound Obstet Gynecol 2020;56:298–312.

6. Lees CC, Stampalija T, Hecher K. Diagnosis and management of fetal growth restriction: the ISUOG guideline and comparison with the SMFM guideline. Ultrasound Obstet Gynecol 2021;57:884–7.

7. Lees CC, Romero R, Stampalija T, et al. Clinical Opinion: the diagnosis and management of suspected fetal growth restriction: an evidence-based approach. Am J Obstet Gynecol 2022;226:366–78.

8. McCowan LM, Figueras F, Anderson NH. Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy. Am J Obstet Gynecol 2018;218:S855–68.

9. Society for Maternal-Fetal Medicine (SMFM). Electronic address: pubs@smfm.orgMartins JG, Biggio JR, Abuhamad A. Society for Maternal-Fetal Medicine Consult Series #52: diagnosis and management of fetal growth restriction: (Replaces Clinical Guideline Number 3, April 2012). Am J Obstet Gynecol 2020;223. B2–17.

10. Gordijn SJ, Beune IM, Thilaganathan B, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol 2016;48:333–9.

11. Melamed N, Baschat A, Yinon Y, et al. FIGO (International Federation of Gynecology and Obstetrics) initiative on fetal growth: best practice advice for screening, diagnosis, and management of fetal growth restriction. Int J Gynaecol Obstet 2021;152(Suppl1):3–57.

12. Ruiz-Martinez S, Papageorghiou AT, Staines-Urias E, Villar J, Gonzalez De Agüero R, Oros D. Clinical impact of Doppler reference charts on management of small-for-gestational-age fetuses: need for standardization. Ultrasound Obstet Gynecol 2020;56:166–72.

13. Wolf H, Stampalija T, Lees CC. TRUFFLE Study Group. Fetal cerebral blood-flow redistribution: analysis of Doppler reference charts and association of different thresholds with adverse perinatal outcome. Ultrasound Obstet Gynecol 2021;58:705–15.

14. Stampalija T, Ghi T, Rosolen V, et al. Current use and performance of the different fetal growth charts in the Italian population. Eur J Obstet Gynecol Reprod Biol 2020;252:323–9.

15. Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth: a sonographic weight standard. Radiology 1991;181:129–33.

16. Stampalija T, Thornton J, Marlow N, et al. Fetal cerebral Doppler changes and outcome in late preterm fetal growth restriction: prospective cohort study. Ultrasound Obstet Gynecol 2020;56:173–81.

17. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements-a prospective study. Am J Obstet Gynecol 1985;151:333–7.

18. Hadlock FP, Deter RL, Harrist RB, Park SK. Fetal abdominal circumference as a predictor of menstrual age. AJR Am J Roentgenol 1982;139:367–70.

19. Stirnemann J, Villar J, Salomon LJ, et al. International estimated fetal weight standards of the INTERGROWTH-21st Project. Ultrasound Obstet Gynecol 2017;49:478–86.

20. Papageorghiou AT, Ohuma EO, Altman DG, et al. International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. Lancet 2014;384:869–79.

21. Gestation Network. Customised centile calculator, GROW version 8.0.4. 2022. Available at: www.gestation.net. Accessed March 02, 2022.

22. Chitty LS, Altman DG, Henderson A, Campbell S. Charts of fetal size: 3. Abdominal measurements. Br J Obstet Gynaecol 1994;101:125–31.

23. Arduini D, Rizzo G. Normal values of pulsatility index from fetal vessels: a cross-sectional study on 1556 healthy fetuses. J Perinat Med 1990;18:165–72.

24. 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;30:287–96.

25. Kiserud T, Piaggio G, Carroli G, et al. The World Health Organization fetal growth charts: a multinational longitudinal study of ultrasound biometric measurements and estimated fetal weight. PLoS Med 2017;14:e1002220.

26. Villar J, Cheikh Ismail LC, Victora CG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet 2014;384:857–68.

27. Oros D, Ruiz-Martinez S, Staines-Urias E, et al. Reference ranges for Doppler indices of umbilical and fetal middle cerebral arteries and cerebroplacental ratio: systematic review. Ultrasound Obstet Gynecol 2019;53:454–64.

28. Mathewlynn S, Impey L, Ioannou C. Detection of small- and large-for-gestational age using different combinations of prenatal and postnatal charts. Ultrasound Obstet Gynecol 2022;60:373–80.

29. Vieira MC, Relph S, Persson M, Seed PT, Pasupathy D. Determination of birth-weight centile thresholds associated with adverse perinatal outcomes using population, customised, and Intergrowth charts: a Swedish population-based cohort study. PLOS Med 2019;16:e1002902.

30. Strassberg ER, Schuster M, Rajaram AM, et al. Comparing diagnosis of fetal growth restriction and the potential impact on management and outcomes using different growth curves. J Ultrasound Med 2019;38:3273–81.

31. Combs CA, Castillo R, Kline C, et al. Choice of standards for sonographic fetal abdominal circumference percentile. Am J Obstet Gynecol MFM 2022;4:100732.

32. Schreiber V, Hurst C, da Silva Costa, Stoke R, Turner J, Kumar S. Definitions matter: detection rates and perinatal outcome for infants classified prenatally as having late fetal growth restriction using SMFM biometric vs ISUOG/Delphi consensus criteria. Ultrasound Obstet Gynecol 2023;61:377–85.

33. Roeckner JT, Pressman K, Odibo L, Duncan JR, Odibo AO. Outcome-based comparison of SMFM and ISUOG definitions of fetal growth restriction. Ultrasound Obstet Gynecol 2021;57:925–30.

34. Gordijn SJ, Ganzevoort W. Search for the best prediction model, definition and growth charts for fetal growth restriction using a composite of adverse perinatal outcomes: a catch-22? Ultrasound Obstet Gynecol 2022;60:305–6.

Author and article information

From the Institute of Reproductive and Developmental Biology, Department of Metabolism, Digestion and Reproduction, Imperial College London, London, United Kingdom (Drs Mylrea-Foley and Lees); Department of Fetal Medicine, Queen Charlotte's and Chelsea Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom (Drs Mylrea-Foley and Lees); Elizabeth Garrett Anderson Institute for Women's Health, University College London, London, United Kingdom (Dr Napolitano); Fetal Medicine Unit, University College London Hospitals NHS Foundation Trust, London, United Kingdom (Dr Napolitano); Department of Obstetrics and Gynecology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands (Dr Gordijn); Department of Obstetrics and Gynecology, Amsterdam University Medical Center (Location AMC), University of Amsterdam, Amsterdam, The Netherlands (Dr Wolf); Unit of Fetal

Medicine and Prenatal Diagnosis, Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste, Italy (Dr Stampalija); Department of Medicine, Surgery and Health Sciences, University of Trieste, Trieste, Italy (Dr Stampalija).

Received May 18, 2023; revised July 26, 2023; accepted Aug. 1, 2023.

The authors report no conflict of interest.

C.C.L. is supported by the UK National Institute for Health and Care Research Biomedical Research Centre based at Imperial College Healthcare National Health Service Trust and Imperial College London.

Pavel Calda (PC) is supported by Czech Ministry of Health grant No MH CZ-DRO-VFN64165.

Results of this study were presented in part at the 32nd World Congress on Ultrasound in Obstetrics and Gynecology, London, United Kingdom, September 16–18, 2022.

Corresponding author: Christoph C. Lees, MD. c.lees@imperial.ac.uk