REGULAR ARTICLE

Variation in term birthweight across European countries affects the prevalence of small for gestational age among very preterm infants

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ABSTRACT

Aim: This study assessed the prevalence of small for gestational age (SGA) among very preterm (VPT) infants using national and European intrauterine references.

Methods: We generated country-specific and common European intrauterine growth references for 11 European countries, according to Gardosi's approach and Hadlock's foetal growth model, using national data on birthweights by sex. These references were applied to the Effective Perinatal Intensive Care in Europe (EPICE) cohort, which comprised 7766 live VPT births without severe congenital anomalies under 32 weeks of gestation in 2011–2012, to estimate the prevalence of infants with SGA birthweights, namely those below the 10th percentile.

Results: The SGA prevalence was 31.8% with country-specific references and 34.0% with common European references. The European references yielded a 10-point difference in the SGA prevalence between countries with lower term birthweights (39.9%) – Portugal, Italy and France – and higher term birthweights, namely Denmark, the Netherlands, Sweden (28.9%; $p < 0.001$). This was not observed with country-specific references, where the respective figures were 32.4% and 33.9% ($p = 0.34$), respectively.

Conclusion: One-third of VPT infants were SGA according to intrauterine references. Common European references showed significant differences in SGA prevalence between countries with high and low-term birthweights.

INTRODUCTION

Neonatal growth references based on birthweight are not appropriate for very preterm (VPT) infants, who are more likely to have abnormal foetal growth than infants born at term. Intra-uterine growth references make it possible to avoid this bias, as they are based on estimated foetal weights calculated from ultrasound measures in normal pregnancies ending at term. Between 25% and 35% of VPT infants are

classified as small for gestational age (SGA) when intra-uterine curves are used, as they have a birthweight below

Abbreviations

CA, Congenital anomalies; CV, Coefficient of variation; EPICE, Effective Perinatal Intensive Care in Europe; FGR, Foetal growth restriction; GA, Gestational age; HELLP, Haemolysis, elevated liver enzymes, low platelet count; SGA, Small for gestational age; VPT, Very preterm.

Key notes

- We assessed the prevalence of small for gestational age (SGA) among 7766 very preterm infants from 11 countries in the Effective Perinatal Intensive Care in Europe cohort.
- We compared European intra-uterine growth references with national references that adjusted for term birthweight in each country.
- When common European references were used, SGA was more prevalent in countries with low-term birthweight than in countries with high-term birthweight.

the 10th percentile (1–4). Moreover, using intra-uterine curves instead of neonatal growth curves improves predictions of infant mortality and morbidity risks (5,6).

Nonetheless, many studies of SGA among VPT infants continue to use birthweight references (7,8). This is probably explained by the availability of national birthweight references in most countries, whereas, with some exceptions (4,9), national intra-uterine references are lacking. One approach to generating national intra-uterine references has been to adapt methods designed to customise individual growth references (10,11). This method, proposed by Gardosi in the 1990s, models foetal growth using Hadlock's intra-uterine references (12), and adjusts them for individual physiological factors, such as maternal parity, height, weight and ethnicity (13). Population-level parameters may be used as well (10,11). This methodology has been used to compare SGA across countries (11), but it has not been specifically applied to VPT infants.

Whether the population parameters should be national or international is also a matter of debate. The Intergrowth 21st Project, which collected foetal parameters in samples of healthy pregnancies in eight countries to develop one common set of references (14), is based on the hypothesis that, when mothers' nutritional and health needs are met, foetal growth is similar across geographical and ethnic settings (15). However, this hypothesis has not been tested, and it is not known whether country-level differences in birthweight affect percentiles for VPT infants.

This study aimed to describe the prevalence of SGA among VPT infants using Gardosi's methodology, overall and for key subgroups, and to evaluate the impact of using country-specific versus common European references.

METHODS

Data

This analysis used data from two European projects: Euro-Peristat and Effective Perinatal Intensive Care in Europe (EPICE).

The Euro-Peristat project aims to monitor perinatal health in European countries using standardised indicators computed from routinely collected population-based data. It has produced two reports on the health and care of pregnant women and babies in Europe based on 2004 and 2010 data (16). In 2010, 29 countries participated in Euro-Peristat. Data on average birthweights by sex, and standard deviations, were collected for live births at 40 weeks of gestation. Gestational age (GA) was defined as the best obstetric estimate using the last menstrual period and ultrasound measures, and the data were requested in completed weeks. Most European countries used first-trimester ultrasounds for pregnancy dating in 2010.

The EPICE project aims to assess the use of evidence-based medicine for the care of very preterm infants (17). In 2011–2012, a geographically defined cohort of VPT stillbirths and live births from 22 + 0 weeks to 31 + 6 weeks of gestation was established in 19 European regions in 11 countries: Belgium (Flanders); Denmark (the Eastern

Region); Estonia (entire country); France (Burgundy, Ile-de-France and the Northern regions), Germany (Hesse and Saarland); Italy (Emilia-Romagna, Lazio and Marche regions); the Netherlands (Central and Eastern regions); Poland (Wielkopolska); Portugal (Lisbon and Northern regions); Sweden (Stockholm County) and the UK (East Midlands, Northern and Yorkshire and Humber regions). Data were collected prospectively on births between April 2011 and September 2012 over a 12-month period in 10 countries and six months in France. More than 850 000 births took place in the EPICE Regions in 2011. GA was defined based on the best obstetric assessment, using information on the last menstrual period and ultrasound measures, and collected as weeks and days. When there were several estimates, the following hierarchy was used to determine GA for the study: in vitro fertilisation treatment, ultrasound based on the earliest estimate, the last menstrual period, fundal height measurement and neonatal assessment at birth. All participating regions used first-trimester ultrasounds for pregnancies in 2011–2012.

Study population

The EPICE cohort comprised 10 329 total births, of which 7900 were live births. Our inclusion criteria for this study were a live birth without a severe congenital anomaly (CA). We excluded stillbirths, because birth can occur several days or more after foetal death, complicating the assessment of their birthweight for gestational age. Infants with severe CA were excluded ($n = 126$, 1.6%) because CA can have an impact on foetal weight. Babies with missing birthweight ($n = 2$) and missing or indeterminate sex ($n = 6$) were also excluded. The final study sample comprised 7766 infants.

Analysis strategy

To develop intra-uterine growth references charts, we adapted the approach proposed by Gardosi, which is based on Hadlock's foetal growth equation ($\log(\text{expected foetal weight}) = 0.578 + 0.332 * \text{GA} - 0.00354 * \text{GA}^2$). Gardosi models the growth trajectory generated by this formula so that it can be applied to any expected birthweight at 40 weeks of gestation and used to derive the expected birthweight at each week of gestation. In customised models, expected birthweight takes into account individual parameters for each infant, namely the mother's height, weight, parity and ethnicity. However, the model can also be applied to an expected birthweight in a population of births (10,11). This expected, or mean birthweight at term, can be interpreted as the 50th percentile, because the distribution of birthweight is assumed to be normal. The coefficient of variation – the standard deviation divided by the mean – based on the standard deviation of birthweight observed in the population at term is used to compute the other percentiles.

Using this methodology and the Euro-Peristat data on mean birthweights at 40 completed weeks of gestation in European countries, we created separate country-specific references for boys and girls for the 11 countries in the EPICE project. We also created a common European

reference based on the median value for average birthweight at 40 weeks in the 11 countries. We used a coefficient of variation corresponding to the median value in participating countries for all the models (12%). Appendix S1 provides a detailed explanation and the equations for deriving the common and country-specific references.

We first compared the 3rd, 10th, 50th, 90th and 97th percentiles across the countries and with the common European model. We then applied our references to the EPICE population of VPT infants and calculated the proportions of SGA infants according to both the country-specific and the common references. We defined SGA as a birthweight <10th percentile, severe SGA as <3rd percentile and moderate SGA as 3rd–<10th percentile. All other infants, with birthweights $\geq$ 10th percentile, were classified as not SGA.

We computed rates of SGA for the entire cohort, and by multiplicity: singletons, twins and higher order multiples. Because growth restriction is itself a cause of medically indicated very preterm delivery, we also computed rates of SGA for a subgroup of infants whose foetal growth restriction (FGR) was unlikely to be the direct cause of their preterm birth. We defined this group as infants with a spontaneous onset of delivery and without an antenatal diagnosis of FGR or pre-eclampsia, eclampsia or haemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome. Diagnosis of FGR was mentioned in the medical records as a suspicion of foetal growth restriction. Pre-eclampsia was defined as proteinuria and systolic blood pressure $\geq$ 140 mmHg and, or, diastolic blood pressure $\geq$ 90 mmHg occurring after gestational week 20 + 0 in a woman who was normotensive before she became pregnant. Proteinuria was defined as $\geq$ 300 mg/L protein in a random specimen or an excretion of 300 mg over 24 hours. Hypertension had to be confirmed by two separate measurements. HELLP syndrome was defined as a cluster of laboratory abnormalities including serum lactic dehydrogenase $>$ 600 U/L, serum aspartate aminotransferase or serum alanine aminotransferase $>$ 70 U/L and a platelet count of $<$ 100 000/mm³. Eclampsia was defined as the onset of seizures in a woman with pre-eclampsia.

We then assessed the impact of using country-specific versus common references by computing the proportion of infants whose SGA status changed between these two references. We also carried out these comparisons for three groups of countries defined by their birthweight at term – high, medium and low – which were identified by dividing the difference between the maximum and minimum country-level birthweights into three intervals.

In a final step, we assessed the concordance of our model with Marsal's intra-uterine references (4) in the EPICE Swedish region. These references were based on 798 ultrasound measurements from 86 low-risk pregnancies, which showed that the 50th percentile for birthweight at 40 weeks of gestation was 3717 g for boys and 3595 g for girls. These were almost identical to the Euro-Peristat mean birthweights at 40 weeks of GA in Sweden. We compared the 3rd, 10th, 50th and 90th percentiles of the published

intra-uterine curves with the Swedish references generated by our models and then compared the rates of SGA generated from these references among Swedish infants in the EPICE cohort (18).

Statistical analysis

We used chi-square tests to compare rates of SGA by country group, country and multiplicity. The association of SGA rates with term birthweight was assessed using logistic regression, with the country group as an ordinal variable, and also by representing each country by its mean term birthweight. We computed Kappa statistics to measure the degree of concordance between the two methods of SGA classifications: overall and by country. The analyses were carried out using Stata 13.0 SE (Stata Corporation, College Station, TX, USA).

RESULTS

Table 1 provides the mean birthweights and standard deviations at 40 weeks of gestation for girls and boys, as obtained by Euro-Peristat, in the 11 countries included in the EPICE cohort. Countries are sorted by the mean birthweight at 40 weeks for girls and boys. For boys, these ranged from 3440 g in Portugal and 3478 g in Italy to 3717 g in Sweden and 3751 g in Estonia. For girls, the range was from 3300 g in Portugal and 3332 g in Italy to 3598 g in Sweden and 3587 g in Estonia. The median for the 11 countries was 3611 g for boys and 3460 g for girls. Most standard deviations fell between the range of 410 and 450 g for boys and 390 and 430 g for girls, yielding coefficients of variation close to 12%. Countries were

Table 1 Means, standard deviations and coefficients of variation (CV) for birthweight at 40 completed weeks of gestation in participating countries in 2010: data from the Euro-Peristat project

Country*	N†	Males			Females		
		Birthweight at 40 weeks			Birthweight at 40 weeks		
		Mean	SD	CV (%)	Mean	SD	CV (%)
Portugal	21 305	3440	454	13.2	3300	455	13.8
Italy	130 671	3478	417	12.0	3332	399	12.0
France‡	3999	3512	412	11.7	3379	394	11.7
UK: England	195 573	3587	443	12.4	3447	426	12.4
Poland	131 573	3603	444	12.3	3440	424	12.3
Belgium (Flanders)	19 782	3611	425	11.8	3460	401	11.6
Germany	177 781	3624	428	11.8	3475	415	11.9
Denmark	17 555	3697	443	12.0	3565	429	12.0
The Netherlands	47 591	3697	450	12.2	3552	433	12.2
Sweden	31 683	3717	447	12.0	3598	436	12.1
Estonia	4962	3751	432	11.5	3587	421	11.7
Median value	–	3611	443	12.0	3460	424	12.0

*Countries sorted by the average of male and female mean birthweight values as data in Euro-Peristat were provided separately for males and females.

†Number of singleton births at 40 weeks of GA.

‡From a representative national sample of births.

divided into low birthweight for Portugal, Italy and France, medium birthweights for England, Poland, Belgium and Germany and high birthweights for Denmark, the Netherlands, Sweden and Estonia).

The mean gestational age in our sample was 28.4 weeks, and the mean birthweight was 1192 g (Table 2). More than 30% of the infants were from multifoetal pregnancies. Antenatal detection of foetal growth restriction and hypertensive diseases of pregnancy were common (16.2% and 14.7% respectively) and 40.6% of the deliveries resulted from a prelabour Caesarean. Infants at lower risk of FGR constituted 56.5% of the sample and this was defined as the spontaneous onset of delivery without suspicion of FGR or preeclampsia, eclampsia or HELLP.

Figure 1 illustrates the growth trajectory and shows the 3rd, 10th, 50th, 90th and 97th percentiles for girls and boys using values generated by the common European model. Table S1 of Appendix S1 provides values for all the country-specific and common percentiles for each completed week of GA by sex. The country-specific percentiles were different between countries with low and high-term birthweights. The 10th percentile at 31 weeks, for instance, was 110–130 g higher in the highest versus lowest birthweight countries. This means that the 10th percentile values in Portugal and in Italy were close to the 3rd percentile values in Estonia and Sweden across all the gestational ages considered in this study.

Table 3 describes rates of SGA for the EPICE cohort. Based on the country-specific references, 31.8% of the infants were SGA, with 20.5% under the 3rd percentile and 11.4% between the 3rd and 10th percentiles. While rates of

SGA <10th percentile were not significantly different for singletons and twins, more singleton SGA infants were severely SGA compared to twins, whereas twins and triplets were more likely to have a birthweight between the 3rd and 10th percentile. When pregnancy complications associated with FGR and nonspontaneous onset births were excluded, the rates of SGA declined to 14.8% of all births for the country-specific references and to 11.0% of singletons. In this population, twins were consistently more likely to be SGA. Overall, the rate of SGA <10th percentile was higher between 28 and 31 weeks of GA (1918/5294, 36.2%) than before 28 weeks of GA (579/2472, 23.4%; $p < 0.001$). Patterns of multiplicity, risk status and gestational age group were similar when using common European references, although the percentage of SGA was slightly higher (34.0% vs 31.8%).

Table 4 presents the rates of SGA using country-specific and common references by individual country and country birthweight group. When the common references were used between 4.1% and 15.2% of infants were reclassified in high and low birthweight countries, leading to a 10 point difference in SGA prevalence between high versus low birthweight countries (38.9%, 31.3% and 28.9%, respectively). The p for trend was <0.001 , and p value was $p < 0.001$ when we compared high and low birthweight countries. This was not the case for the country-specific references: the p for trend was 0.96, the p value for the comparison between high to low birthweight countries was $p = 0.34$, and the p value for the comparison of the three groups was $p = 0.03$. For individual countries, there was a strong trend associating SGA rates with average birthweight at term when the common references were used ($p < 0.001$), which was not significant using country-specific references ($p = 0.94$). The Kappa statistics, which provided a measure of concordance between these classifications, were very high in most cases, but they were lower for the low and high birthweight country groups than for the medium group and in some individual countries, such as Portugal, Estonia and Sweden. Table 4 also illustrates the variability in rates of SGA by country in the regions participating in EPICE, even when country-specific references were used, from lows of 25.8% and 28.4% in Poland and Belgium to highs of 36.9% and 37.5% in Germany and Denmark, respectively.

Figure 2 compares the model used for this analysis, based on Hadlock's references and Gardosi approach, labelled the Hadlock-Gardosi Model, with the Swedish references proposed by Marsal et al. for girls and boys (4). The Marsal et al.'s curve was slightly higher than the Hadlock-Gardosi Model, especially for girls, and the differences were more marked for the 50th and 90th percentiles than for the 3rd and 10th. Overall 35.1% of Swedish VPT infants were under the 10th percentile using Swedish national references versus 31.5% for the Hadlock-Gardosi model and 23.9% and 21.5%, respectively were under the 3rd percentile (Table S2 of Appendix S1). The proportions were closer for boys (32.4% vs 31.7%) than girls (38.4% vs 31.3%). Concordance was 96.4%: 99.3% for boys and 92.1% for girls.

Table 2 Characteristics of live births without severe congenital anomalies in the EPICE cohort

	Live births (n = 7766)	
	Mean	SD
Gestational age (weeks)	28.4	2.4
Birthweight (g)	1192	401
	N	%
Male	4204	54.1
Type of gestation		
Singleton	5344	68.8
Multiple	2144	27.6
Triplet/quadruplet	276	3.6
Antenatal suspicion of FGR	1233	16.2
Pre-eclampsia/Eclampsia/HELLP	1145	14.7
Mode of delivery		
Prelabour Caesarean	3114	40.6
Intrapartum Caesarean	1883	24.5
Vaginal delivery	2683	34.9
Spontaneous onset of delivery with no antenatal suspicion of FGR or pre-eclampsia/eclampsia/HELLP	4344	56.5

Variables do not sum up to total because of missing observations (2 for multiples, 6 for sex – also includes undetermined sex – and <1% for other variables, 1.2% for composite variable on FGR).

Figure 1 Percentile values for intra-uterine growth references for very preterm boys and girls using the common European model. Note: 1. Gestational age corresponds to exact weeks of gestation, that is 22 = 22 + 0 days.

Table 3 Rates of SGA for all infants and infants at lower risk of FGR by multiplicity using country-specific and common European references

	n	Country-specific references			Common European references		
		<3rd p %	3rd–9th p %	Total <10th p %	<3rd P %	3rd–9th p %	Total <10th p %
Overall by multiplicity	7766	20.5	11.4	31.8	21.8	12.2	34.0
Singleton	5344	22.1	10.0	32.0	23.4	10.3	33.8
Twin	2144	16.3	14.3	30.6	17.5	15.9	33.4
Triplet/quadruplet	276	21.7	15.6	37.3	23.2	18.5	41.7
p value (twins vs. singletons)		<0.01	<0.001	0.226	<0.001	<0.001	0.759
p value (triplets vs. singletons)		0.670	0.002	0.067	0.610	<0.001	0.012
Lower risk of FGR* by multiplicity	4344	5.7	9.1	14.8	6.3	10.6	16.9
Singleton	2854	4.1	6.8	11.0	4.7	7.9	12.5
Multiple	1347	8.3	13.4	21.8	9.2	15.5	24.7
Triplet/quadruplet	141	10.6	14.2	24.8	10.6	19.1	29.8
p value (twins vs. singletons)		<0.010	<0.001	<0.001	<0.001	<0.001	<0.001
p value (triplets vs. singletons)		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

*Spontaneous onset of delivery with no antenatal suspicion of FGR or pre-eclampsia/eclampsia/HELLP.

DISCUSSION

We constructed country-specific and common European intra-uterine growth references for VPT infants using data on birthweight at 40 weeks of gestation in 11 European countries. Mean birthweight at term differed by more than 300 g across countries and this led to substantial differences

in the 3rd and 10th percentiles for VPT infants in high versus low-term birthweight countries. Using country-specific references, 32% of VPT infants in our European cohort were SGA and most had birthweights under the 3rd percentile. The use of a common versus country-specific reference classified a larger proportion of infants as SGA in

Table 4 Differences between SGA classifications by country and country group using country-specific versus common European references

	N	Country-specific references			Common European references			Change SGA status %	Kappa Statistic
		<3rd P %	3rd-9th p %	Total <10th p %	<3rd P %	3rd-9th p %	Total <10th p %		
Total	7766	20.5	11.4	31.8	21.8	12.2	34.0	6.0	0.92
Individual countries*									
Portugal	719	21.4	11.7	33.1	26.8	15.6	42.4	14.7	0.74
Italy	1111	19.4	11.7	31.1	24.3	13.6	37.9	11.8	0.81
France	1290	22.2	10.9	33.2	24.8	12.9	37.8	7.1	0.85
UK	1714	18.6	11.1	29.8	19.3	11.5	30.8	1.8	0.96
Poland	299	13.0	12.7	25.8	13.4	13.7	27.1	1.7	0.91
Belgium	749	17.4	11.1	28.4	17.4	11.9	29.2	0.8	0.99
Germany	731	24.6	12.3	36.9	24.1	12.2	36.3	1.2	0.98
Denmark	347	26.2	11.2	37.5	24.2	8.4	32.6	6.9	0.85
The Netherlands	392	23.7	9.2	32.9	21.9	8.7	30.6	4.1	0.90
Sweden	263	21.3	10.3	31.6	16.3	9.9	26.2	10.3	0.78
Estonia	151	17.2	15.2	32.5	13.9	6.6	20.5	15.2	0.75
p value (chi-square)				<0.001			<0.001		
p value (test for trend)				0.94			<0.001		
Country groups†									
Low-term birthweight countries	3120	21.0	11.4	32.4	25.1	13.8	38.9	10.5	0.87
Medium-term birthweight countries	3493	19.1	11.5	30.6	19.4	11.9	31.3	1.4	0.98
High-term birthweight countries	1153	23.1	10.8	33.9	20.3	8.6	28.9	7.8	0.88
p value (chi-square)				0.03			<0.001		
p value (test for trend)				0.96			<0.001		

*Countries sorted by average birthweight at 40 weeks of boys and girls.

†Low-term birthweight: Portugal, Italy, France; Medium-term birthweight: England, Poland, Belgium and Germany; High-term birthweight: Denmark, the Netherlands, Sweden and Estonia.

low birthweight countries and a lower proportion in high birthweight countries.

Our study found that about one-third of VPT infants had a birthweight that was less than the 10th percentile, and 20% were less than the 3rd percentile. This is consistent with other research on SGA rates when intra-uterine references were used (1–4). In Sweden, Marsal et al. found that 32% of infants born before 30 weeks of gestation had a birth weight below the 3rd percentile, compared to 11% at 30–36 weeks (4). Zaw et al., who studied infants born before 34 weeks of gestation, found that 12% had birthweights under the 10th percentile according to neonatal standards, but this rose to 23% when foetal growth standards were used (1). Ferdynus et al. showed that 25% of French births under 37 weeks were under the 10th percentile of foetal weight standards versus 11% by birth weight standards (19). In our sample, the prevalence of SGA was lower when gestational age was under 28 weeks, which may reflect fewer indicated deliveries for growth restriction among extremely preterm infants. The SGA prevalence also differed substantially by multiplicity and pregnancy complications, which is in line with current knowledge about the impact of these clinical parameters on growth restriction in the setting of prematurity (20).

We found a strong association between rates of SGA and mean term birthweight when a common reference was used. These results call into question the use of common

growth norms, as advocated by the Intergrowth 21st project (15). Basing evaluations of SGA on our common model would require the assumption that the large differences in term birthweight in Europe resulted primarily from abnormal growth as opposed to physiological differences in population size. Previous European research has provided support for this latter assertion, as the optimal birthweight – defined as the birthweight at which mortality is lowest – is lower in populations with lower term birthweights (21). Other studies have shown that using population-adjusted references more adequately identifies infants at risk of poor outcome (22). The National Institute of Child Health and Development Fetal Growth Studies also contested this claim with its recently published references by race and ethnicity in the United States (23).

Even when we used country-specific references, we found heterogeneity in the SGA prevalence between EPICE regions. These differences could have resulted from population characteristics, such as maternal age or the multiple pregnancy rate, which vary in Europe and impact on the prevalence and causes of preterm birth (24). Different healthcare policies and practices, including prenatal care and screening, the criteria for inducing delivery because of foetal growth impairment and approaches to ethical decision-making may also play a role. The contribution of these factors to rates of SGA among very preterm infants is an important area for further research. The existence of this variability across countries provides further justification for

Figure 2 Comparison between the 3rd, 10th, 50th and 90th percentiles of Hadlock-Gardosi (HG) model (2a) and Marsal's Swedish intra-uterine references (2b) for males and females. (a) Males – Hadlock-Gardosi (solid line), Marsal (dotted line). (b) Females – Hadlock-Gardosi (solid line), Marsal (dotted line). Note: 1 corresponds to exact weeks of gestation, that is 22 = 22 + 0 days.

avoiding neonatal birthweight standards, which, by definition, classify 10% of the population under the 10th percentile and therefore do not make it possible to assess or investigate these differences.

Our study had potential limitations. The first limitation was that we assumed that mean term birthweights could be used to create country-specific references, but this may not have been appropriate for all infants, especially in countries with large migrant populations. Taking into account maternal height, weight and ethnicity could make it possible to refine these references, but these data were not available. Furthermore, studies have shown that these maternal characteristics only account for a small proportion of the birthweight variability, especially for VPT infants (2). The second limitation was that our references relied on the untested assumption that Hadlock's formula could be

transposed to any population and that the coefficient of variation remains constant across all gestational ages. Nevertheless, the Hadlock's growth references and Gardosi's customised model are widely used in multiple countries for clinical care and research (25) and many intra-uterine growth models assume that the coefficient of variation is constant (4,26,27). We were able to compare our model with Swedish national intra-uterine references for the Swedish infants in our sample and observed high concordance for SGA prevalence, despite slight differences in percentile values, which have been noted in other comparisons (9). These differences may result from the use of various statistical methods (28) and changes in foetal growth over time. The publication of intra-uterine curves by the Intergrowth 21st project (29) the World Health Organization study of foetal growth (30) and the

National Institute of Child Health and Development foetal growth project (23) provides an opportunity for future comparative studies on the assumptions used in these models. Finally, future investigations should go beyond a statistical definition of SGA and include other clinical measures to assess growth restrictions, such as Doppler measurements, in order to verify the appropriateness of specific thresholds across populations using more specific measures of morbidity.

CONCLUSION

This study constructed country-specific intra-uterine growth references for 11 countries in Europe based on the Hadlock-Gardosi model and illustrated the high proportions of very preterm infants classified as SGA, and, in particular, as severely SGA with a birthweight under the 3rd percentile when intra-uterine references were used. We showed that the large variation in term birthweight across European countries affected birthweight references for VPT infants, calling into question the use of common references for the assessment of SGA in VPT infants in Europe. Our results also highlight the need for cross-national studies on the causes and consequences of foetal growth restriction in this high-risk population.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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APPENDIX

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1 Modeling intrauterine growth references.