DOI: 10.1111/1471-0528.12282
www.bjog.org

Comparison of the ability of alternative birthweight and fetal weight standards to identify preterm newborns at increased risk of perinatal death

C Ferdynus,[a,b] C Quantin,[c,d] M Abrahamowicz,[e,f] A Burguet,[g,h,i] P Sagot,[a,j] J-B Gouyon[a,k]

[a] Centre d'Epidémiologie des Populations, Université de Bourgogne, Dijon, France [b] Unité de Soutien Méthodologique, University Hospital, Saint Denis de la Réunion, France [c] CHRU, Service de Biostatistique et d'Informatique Médicale, CHU de Dijon, France [d] Inserm, U866, Dijon, Université de Bourgogne, Dijon, France [e] Department of Epidemiology and Biostatistics, McGill University, Montreal, QC, Canada [f] Department of Biostatistics, Réunion University (France) and CHU de La Reunion, Centre d'Etudes Périnatales de l'Océan Indien, Saint-Pierre Cedex, France [g] Inserm, CIE1, Dijon, France [h] CHRU Dijon, Centre d'Investigation Clinique–Epidémiologie Clinique/Essais Cliniques, Dijon, France [i] Université de Bourgogne, Dijon, France [j] Department of Obstetrics and Gynaecology, University Hospital, Dijon, France [k] Department of Paediatrics, University Hospital, Dijon, France

Correspondence: C Ferdynus, Unité de Soutien Méthodologique, CHU de la Réunion–Site Félix Guyon, Route de Bellepierre, 97405 Saint Denis Cedex, France. Email cyril.ferdynus@chu-reunion.fr

Accepted 10 March 2013. Published Online 31 May 2013.

Objective To compare prediction of perinatal deaths among preterm infants based on fetal weight standards versus a new subpopulation-based birthweight standard.

Design Population-based cohort study.

Setting France.

Population A total of 9100 preterm singletons, born between 24 and 36 weeks of gestation in 2000–09, in Burgundy (France).

Methods We first classified all newborns as either small for gestational age (SGA) or not, based on alternative fetal weight or birthweight standards, including a new birthweight standard that excludes infants born to mothers with disease related to the weight of a fetus. Based on discrepancies between the different classifications, we then divided the newborns into four groups, and compared their risks of stillbirth and in-hospital death, using a generalised linear model with relative risks (RR).

Main outcome measures Perinatal deaths, including, in separate analyses, stillbirths and in-hospital deaths.

Results The preterm infants classified as SGA by our new subpopulation-based birthweight standard but not by the conventional birthweight standard had a significantly higher risk of both stillbirth (RR = 2.6; 95% confidence interval [95% CI] = 1.9–3.6) and in-hospital death (RR = 2.8; 95% CI = 1.8–4.5). In contrast, no risk increase was found for infants classified as SGA by the fetal standard only (RR = 1.1; 95% CI = 0.7–1.7 for stillbirths, and RR = 0.5; 95% CI = 0.3–1.3 for in-hospital deaths).

Conclusions Our subpopulation-based birthweight standard identified a subgroup of preterm newborns who have significantly increased risks of perinatal death but are not classified as SGA by the conventional birthweight standard. In contrast, the subgroup classified as SGA by the fetal standards only, but not by our subpopulation-based birthweight standard, had no increased risk of mortality, compared with non-SGA infants.

Keywords Birthweight, fetal growth, growth standard, in-hospital death, intrauterine growth restriction, small for gestational age, stillbirth.

Please cite this paper as: FerdynusC, Quantin C, Abrahamowicz M, Burguet A, Sagot P, Gouyon J-B. Comparison of the ability of alternative birthweight and fetal weight standards to identify preterm newborns at increased risk of perinatal death. BJOG 2013; DOI: 10.1111/1471-0528.12282.

Introduction

There is a long-standing debate regarding the choice of the optimal growth standard for detecting newborns with intrauterine growth restriction. It is now well established that neonatal growth standards, derived from the whole population that includes infants born to women with maternal diseases that adversely affect the weight of fetuses,[1,2] tend to lower the cutoff points for identification of small-for-gestational-age (SGA) newborns. This may lead to misclassification of an important fraction of newborns with actual intrauterine growth restriction as Appropriate

© 2013 RCOG

for Gestational Age (AGA), especially among preterm births.[3–5] For this reason, it has been recommended to use fetal weight standards, instead of neonatal growth standards, to improve the identification of SGA preterm infants who are at an increased risk of perinatal morbidity or mortality.[6–8] Unlike neonatal growth standards, which are estimated from the birthweights of infants born alive, fetal weight standards are obtained by estimating the fetal weights from ultrasonic measurements of fetal parts and then using these measurements in regression equations, such as that proposed by Hadlock et al.[9]

On the other hand, all studies that concluded that fetal weight standards perform better in predicting perinatal morbidity and mortality among SGA newborns have compared them with conventional birthweight standards, based on the entire population of newborns.[6–8] Yet, a recent study found that a revised neonatal birthweight standard for SGA, based on a subpopulation that excluded pregnancies of mothers with gestational or chronic diseases that could affect the weight of the fetus, was also superior to a conventional neonatal birthweight standard in the ability to identify preterm newborns at risk of neonatal morbidity.[5] To the best of our knowledge, this novel subpopulation-based birthweight standard has not yet been compared with fetal weight standards. Therefore, the aim of this study was to assess the ability of the subpopulation birthweight standard to identify preterm infants at an increased risk of perinatal death and to compare it with the conventional birthweight standard and with fetal weight standards.

Patients and methods

Study population

The study population consisted of all singleton preterm births, between 24 and 36 weeks of gestation, without chromosomal aberrations, recorded in the Burgundy Perinatal Network database, between January 2000 and December 2009. This database contains information on all live births and stillbirths that occur in the French region of Burgundy at a gestational age ≥22 weeks, and is used to regularly assess the Burgundy Perinatal Network procedures.[10,11] This database contains the data on more than 99.9% of all births in the region.[10,11] In France, gestational age is assessed on the basis of the mother's last menstrual period and confirmed or modified, when necessary, by routine early antenatal ultrasound scan, which is performed for approximately 95% of pregnant women.[12]

Identification of SGA infants based on alternative standards

The birthweight of all newborns in the study population was measured and then compared against the four alternative standards, for a corresponding week of completed gestational age. Specifically, we employed two birthweight and two fetal weight standards. The two birthweight standards were both sex-specific and were calculated according to a previously published method.[5] First, we used (i) a 'conventional' population-based birthweight standard, which was based on sex-specific and gestational-week-specific birthweight distribution of all singletons live births in the entire population. In addition, we also employed (ii) a novel, subpopulation-based birthweight standard, based on sex-specific and gestational-week-specific birthweight distribution in the subpopulation of singleton live births, which excluded births from mothers with maternal diseases related to weight of fetuses (diabetes, maternal hypertension, pre-eclampsia, eclampsia, placental abruption, placenta praevia, presumed chorioamnionitis, oligohydramnios).[5] The two fetal weight standards included: (iii) a non-sex-specific fetal weight standard established from US pregnancies by Hadlock et al.,[13] which is widely used worldwide, and (iv) a sex-specific fetal weight standard, based on pregnancies in France by Salomon et al.[14]

For each of the four standards, the newborns were classified as SGA if their birthweight was below the corresponding 10th centile for a given completed week of gestation and (except for the Hadlock fetal weight standard) sex. The gestational age-specific 10th centiles reported by these alternative weight standards are illustrated in Figure 1 (male) and Figure 2 (female). For both sexes, the two fetal weight standards yield systematically higher values of the corresponding centiles than the two birthweight standards. Among the birthweight standards, the subpopulation-based centiles are always higher than the conventional population-based centiles (Figures 1 and 2).

These systematic differences between the centiles derived from alternative standards allowed us to divide all the newborns in our study population into four mutually exclusive groups, which differed with respect to which standards classified them as SGA. Below, we define the four groups, presented in the order of increasing birthweight, and identify each group by an acronym by which the group is then referred to throughout the manuscript. The four groups are also identified by the boxes, with respective acronyms, in Figures 1 and 2.

(i) SGA_{pop}: newborns whose birthweight was below the 10th centile of the 'conventional' population-based birthweight standard (these newborns are classified as SGA by all standards considered in our analyses);
(ii) SGA_{subpop}-non-SGA_{pop}: newborns whose birthweight was above the 10th centile of the 'conventional' population-based birthweight standard but below the 10th centile of the subpopulation-based birthweight standard (these newborns are not classified as SGA by the

© 2013 RCOG

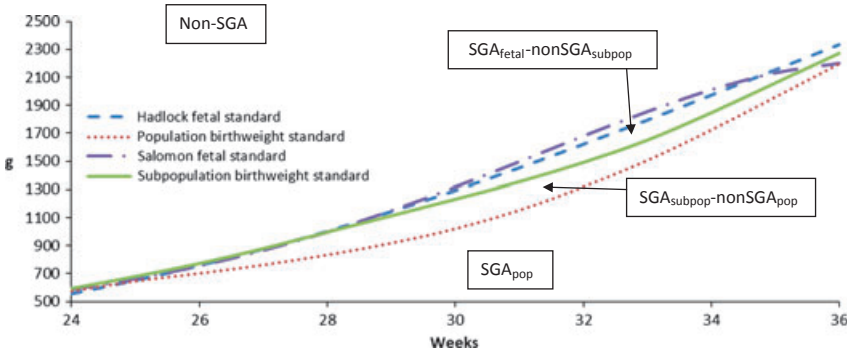

Figure 1. Tenth centiles by gestational age for male newborns of two fetal weight standards (Hadlock, Salomon), a subpopulation birthweight standard and a population birthweight standard.

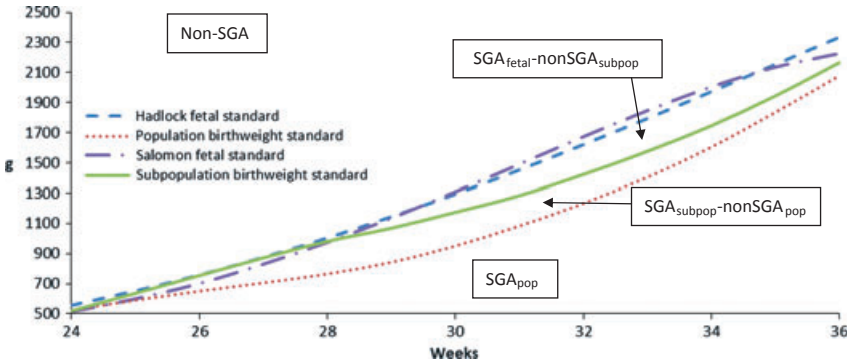

Figure 2. Tenth centiles by gestational age for female newborns of two fetal weight standards (Hadlock, Salomon), a subpopulation birthweight standard and a population birthweight standard.

population-based birthweight standard but are identified as SGA by all other standards considered);

(iii) SGA$_{fetal}$-non-SGA$_{subpop}$: newborns whose birthweight was above the 10th centile of the subpopulation-based birthweight standard but below the 10th centile of the fetal weight standard (classified as SGA only by the fetal standards);

(iv) non-SGA: newborns whose birthweight was above the 10th centile of the fetal weight standard (not identified as SGA by any of the standards considered).

It should be noted that we defined groups (iii) and (iv) in two separate analyses, based on either the fetal weight standard by Hadlock (not sex-specific)[13] or the French (sex-specific) fetal weight standard.[14]

Outcomes

The primary outcomes, assessed in separate analyses, were the occurrence of stillbirth and in-hospital death. Stillbirth was defined as both antepartum and intrapartum fetal deaths. In-hospital death was defined as a death occurring before the newborn was discharged from the hospital.

Statistical analyses

For each of the three SGA groups (i)–(iii), as defined above, we estimated the relative risks (RR) of stillbirth and in-hospital deaths, with 95% confidence intervals (95% CI), compared with the reference group (iv), which consisted of the infants classified as 'non-SGA'. Denominators used for the calculations of the risk of stillbirth, at a given gestational age, were based on the number of continuing pregnancies at risk, at the corresponding gestational age. The number of fetuses at risk is the appropriate denominator in the study of stillbirths because all fetuses not yet born until the end of the previous week are at risk for stillbirth in a given week, whereas, by definition, previous live births or previous stillbirths are no longer at risk of having a stillbirth.[15,16] Conversely, denominators used in the analyses of risk of in-hospital deaths corresponded to the number of live-born infants exclusively in a given gestational age week.

Because Hadlock's intrauterine standard is not sex-specific,[13] a generalised linear model (binomial family with the logarithmic link) was used to estimate sex-adjusted RR for this fetal standard. Differences of risks between different SGA groups (see above) were assessed using contrasts.

© 2013 RCOG

In addition, following the recommendations for reporting of the analyses that assess the accuracy of prediction or diagnosis,[17] we compared the ability of SGA definitions based on the four alternative standards to predict, in separate analyses, stillbirths and in-hospital deaths. To this end, we estimated and compared the sensitivities, specificities and likelihood ratios, with 95% confidence intervals.[18]

Statistical analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA) and R software. All hypotheses were tested at the two-tailed 0.05 significance level.

Results

We included in the analyses 9100 preterm singleton newborns, with gestational age between 24 and 36 weeks of gestation. Mean gestational age was 34.1 ± 2.7 weeks and mean birthweight was 2262 ± 675 g. The proportion of male newborns was 55.3%. The overall rate of stillbirth in this preterm population was 43.0 per 1000 births (95% CI 38.8–47.1) and the overall rate of in-hospital death was 16.2 per 1000 live births (95% CI 13.5–18.8).

Figures 1 and 2 compare the 10th centiles of the two fetal weight standards, with the 'conventional' population-based and subpopulation-based birthweight standards, respectively, for male and female infants. Below 28 weeks of gestation, the 10th centiles of the fetal weight and the subpopulation-based birthweight standards overlap in both male and female infants. After 28 weeks, the fetal weight standards are always above the subpopulation-based birthweight standard. Conversely, the centiles for the 'conventional' population-based birthweight standard were systematically much lower than for the other three standards.

Figure 3 shows the percentages of infants classified into mutually exclusive groups (SGA_{pop}, SGA_{subpop}-non SGA_{pop} and SGA_{fetal}-non SGA_{subpop}), based on the 10th centiles of alternative standards. Overall, about 11.0% of all newborns were classified as SGA by the 'conventional' population-based birthweight standard (SGA_{pop} group). The subpopulation-based birthweight standard classified as SGA an additional 6.5% of all newborns (SGA_{subpop}-non-SGA_{pop} group). Finally, the two fetal weight standards classified as SGA an additional 8.6% (Hadlock) and 7.1% (Salomon) of all newborns, who were not identified as SGA by the subpopulation-based birthweight standard (SGA_{fetal}-non-SGA_{subpop}). As a consequence, as many as 26.0% and 23.8% of all newborns were classified as SGA by the fetal standards of Hadlock et al. and Salomon et al., respectively. Among newborns born before 28 weeks of gestation, only a negligible fraction of infants was reclassified as SGA by the fetal standards only (SGA_{fetal}-non-SGA_{subpop}): 1.3% for the US standard of Hadlock et al. and 0.0% for the French standard of Salomon et al.

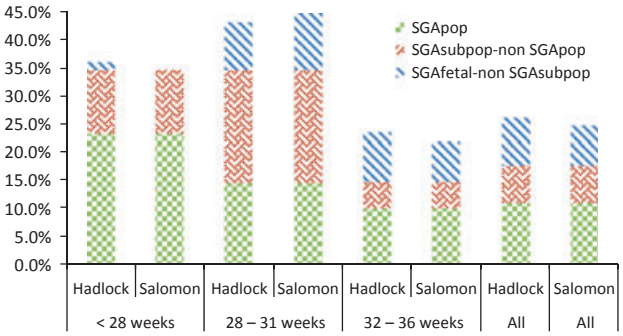

Figure 3. Proportions of newborns classified as non-SGA by all standards, SGA by only fetal standard (Hadlock, Salomon), SGA by the subpopulation-based standard and SGA by both standards among 9100 preterm births from Burgundy (France).

Hence, meaningful discrepancies between SGA classifications based on subpopulation-based birthweight versus the fetal weight standards were limited to those preterm infants who were born between 28 and 36 weeks of gestation.

Relative risks for stillbirth, for different groups compared with the reference group of infants not classified as SGA by any of the standards (non-SGA) are presented in Table 1. Newborns classified as SGA by our subpopulation-based birthweight standard but not by the conventional birthweight standard (SGA_{subpop}-non-SGA_{pop}) had more than twice the risk of stillbirth compared with non-SGA infants (RR = 2.6; 95% CI 1.9–3.6). In contrast, no risk increase, compared with non-SGA infants, was observed among newborns classified as SGA only by the fetal standards but not by the subpopulation-based birthweight standards (SGA_{fetal}-non-SGA_{subpop} group), regardless of the fetal standard used (RR = 1.1; 95% CI 0.7–1.7 with Hadlock's standard and RR = 1.4; 95% CI 0.9–2.1 with Salomon's standard). Additional analyses limited to newborns classified as SGA by the fetal standards, confirmed that the stillbirth risks were statistically significantly higher for those who were also classified as SGA by the subpopulation birthweight standard ($P = 0.0008$ for Hadlock's standard and $P = 0.009$ for Salomon's standard, for comparisons between SGA_{subpop}-non-SGA_{pop} and SGA_{fetal}-non-SGA-sub_{pop} groups).

Relative risks for in-hospital deaths, for different groups compared with the reference group of infants not classified as SGA by any of the standards (non-SGA) are presented in Table 2. Similar to the results or stillbirths, infants classified as SGA only by the subpopulation-based birthweight standard but not by the conventional birthweight standard, based on the entire population of newborns (SGA_{subpop}-non-SGA_{pop}) had more than twice the risk of in-hospital death compared with non-SGA infants

© 2013 RCOG

© 2013 RCOG

Table 1. Relative risks of stillbirths (fetuses at risk approach) among infants classified as SGA by only fetal standard (Hadlock, Salomon), SGA by the subpopulation-based birthweight standard and SGA by both standards among 9100 preterm births from Burgundy (France).

	Fetal standards	Non SGA		SGA_{fetal}-Non SGA_{subpop}			SGA_{subpop}-Non SGA_{pop}			SGA_{pop}		
		At-risk	*n* (risk per 1000)	At-risk	*n* (risk per 1000)	RR	At-risk	*n* (risk per 1000)	RR	At-risk	*n* (risk per 1000)	RR
All preterm	Hadlock	6726	179 (26.6)	779	23 (29.5)	1.1 (0.7–1.7)	593	41 (69.1)	2.6 (1.9–3.6)	1002	148 (147.7)	5.5 (4.5–6.8)
	Salomon	6859	179 (26.1)	646	23 (35.6)	1.4 (0.9–2.1)	593	41 (69.1)	2.7 (1.9–3.7)	1002	148 (147.7)	5.7 (4.6–7.0)
<28 weeks	Hadlock	6726	58 (8.6)	779	2 (2.6)	0.3 (0.1–1.2)	593	6 (10.1)	1.2 (0.5–2.7)	1002	64 (63.9)	7.4 (5.2–10.5)
	Salomon	6859	60 (8.7)	646	0 (0.0)	–	593	6 (10.1)	1.2 (0.5–2.7)	1002	64 (63.9)	7.3 (5.2–10.3)
28–31 weeks	Hadlock	6478	43 (6.6)	774	3 (3.9)	0.6 (0.2–2.0)	549	23 (41.9)	6.4 (3.9–10.6)	912	42 (46.1)	6.9 (4.6–10.6)
	Salomon	6606	43 (6.5)	646	3 (4.6)	0.7 (0.2–2.4)	549	23 (41.9)	6.5 (4.0–10.8)	912	42 (46.1)	7.1 (4.7–10.8)
32–36 weeks	Hadlock	5967	78 (13.1)	699	18 (25.8)	2.0 (1.2–3.3)	367	12 (32.7)	2.5 (1.4–4.6)	783	42 (53.6)	4.1 (2.8–5.9)
	Salomon	6110	76 (12.4)	556	20 (36.0)	2.9 (1.8–4.8)	367	12 (32.7)	2.6 (1.4–4.8)	783	42 (53.6)	4.3 (3.0–6.2)

Table 2. Relative risk of in-hospital death of live birth newborns classified as SGA by only fetal standard (Hadlock, Salomon), SGA by the subpopulation-based birthweight standard and SGA by both standards among 9100 preterm births from Burgundy (France).

	Fetal standards	Non SGA		SGA_{pop}			SGA_{fetal}-Non SGA_{subpop}			SGA_{subpop}-Non SGA_{pop}		
		At-risk	*n* (risk per 1000)	At-risk	*n* (risk per 1000)	RR	At-risk	*n* (risk per 1000)	RR	At-risk	*n* (risk per 1000)	RR
All preterm	Hadlock	6547	91 (13.9)	756	5 (6.6)	0.5 (0.3–1.3)	552	21 (38.0)	2.8 (1.8–4.5)	854	24 (28.1)	2.0 (1.3–3.2)
	Salomon	6680	95 (14.2)	623	1 (1.6)	0.1 (0.02–0.9)	552	21 (38.0)	2.7 (1.7–4.4)	854	24 (28.1)	2.0 (1.3–3.1)
<28 weeks	Hadlock	190	48 (25.3)	3	3 (100.0)	–	38	8 (21.0)	0.9 (0.4–2.1)	26	13 (50.0)	3.0 (1.3–7.0)
	Salomon	193	51 (26.4)	0	0 (0.0)	–	38	8 (21.0)	0.8 (0.4–1.6)	26	13 (50.0)	1.8 (1.2–2.9)
28–31 weeks	Hadlock	468	16 (34.2)	72	1 (13.9)	0.4 (0.1–3.0)	159	13 (81.8)	2.4 (1.2–4.9)	87	4 (46.0)	1.3 (0.5–3.9)
	Salomon	453	16 (35.3)	87	1 (11.5)	0.3 (0.1–2.4)	159	13 (81.8)	2.3 (1.1–4.7)	87	4 (46.0)	1.3 (0.4–3.8)
32–36 weeks	Hadlock	5889	27 (4.6)	681	1 (1.5)	0.3 (0.1–2.5)	355	0 (0.0)	–	741	7 (9.4)	2.0 (0.9–4.7)
	Salomon	6034	28 (4.6)	536	0 (0.0)	–	355	0 (0.0)	–	741	7 (9.4)	2.0 (0.9–4.6)

(RR = 2.8; 95% CI 1.8–4.5). In contrast, for newborns classified as SGA with either fetal weight standard but not by the subpopulation-based birthweight standard (SGA_{fetal}-non-SGA_{subpop} group) there was no evidence of an increased risk of in-hospital death, compared with non-SGA infants (RR = 0.5; 95% CI 0.3–1.3 for the USA, and RR = 0.1; 95% CI 0.02–0.9 for the French fetal standard). However, it should be noted that both estimates were imprecise because of the low number of in-hospital deaths in the SGA_{fetal}-non-SGA_{subpop} group that resulted in wide confidence intervals.

To provide further insights regarding the performance of different standards, Table 3 compares the ability of SGA definitions based on alternative standards to identify newborns with, respectively, stillbirths and in-hospital deaths. The general pattern of results in Table 3 is similar for both outcomes and different GA categories. The sensitivities are generally low, because many outcomes occur in the much larger groups classified, by alternative standards, as non-SGA newborns. On the other hand, specificities are relatively high. This pattern of results reflects mainly the fact that even if the newborns identified as SGA are at higher risk of both outcomes, they represent only a small fraction of the total population. For the same reason, the sensitivity was the lowest and the specificity the highest for the population-based birthweight standard (Table 3), that classified the smallest number of infants as SGA (Figure 3). The subpopulation-based birthweight standard increased sensitivity by more than 10% with only relatively small decreases in specificity (Table 3). As a consequence, the likelihood ratios (LR), that represent the trade-off between sensitivity and specificity,[18,19] were for some subgroups higher for the population-based birthweight standard and for other subgroups for the subpopulation-based birthweight standard (Table 3). However, because of the relatively low number of outcomes, the 95% confidence intervals for all LR are wide, indicating that these differences may be partly the result of sampling errors.

In contrast, the two fetal standards, that classified the highest proportions of newborns as SGA, had considerably lower specificity but only moderately higher sensitivity than the subpopulation-based birthweight standard (Table 3). This resulted in the LRs for the two fetal standards being almost always lower than for the corresponding LRs for the subpopulation-based birthweight standard (Table 3). However, it should be noticed that all LRs shown in Table 3 are <5, which indicates that, regardless of the standard used, newborn weight alone is a poor predictor of individual stillbirths or in-hospital deaths.

Table 3. Sensitivity, specificity and likelihood ratios and their 95% confidence intervals in the prediction of stillbirths and in-hospital death.

Standards	Stillbirths				In-hospital death			
	Se	Sp	LR	95% CI	Se	Sp	LR	95% CI
Population birthweight								
All preterm	0.38	0.90	3.86	3.35–4.45	0.17	0.90	1.76	1.21–2.54
<28 weeks	0.49	0.90	4.71	3.91–5.66	0.18	0.93	2.57	1.25–5.27
28–31 weeks	0.38	0.90	3.74	2.92–4.79	0.12	0.89	1.07	0.41–2.74
32–36 weeks	0.28	0.90	2.90	2.22–3.78	0.20	0.90	2.08	1.07–4.05
Subpopulation birthweight								
All preterm	0.48	0.84	2.99	2.67–3.36	0.32	0.84	2.01	1.58–2.57
<28 weeks	0.54	0.83	3.17	3.17–3.74	0.29	0.77	1.25	0.80–1.96
28–31 weeks	0.59	0.84	3.61	3.06–4.25	0.50	0.70	1.64	1.15–2.34
32–36 weeks	0.36	0.86	2.52	2.02–3.14	0.20	0.86	1.40	0.72–2.72
Fetal (Hadlock)								
All preterm	0.53	0.75	2.14	1.94–2.37	0.34	0.75	1.38	1.09–1.74
<28 weeks	0.52	0.74	2.04	1.72–2.41	0.31	0.77	1.31	0.85–2.03
28–31 weeks	0.61	0.75	2.43	2.09–2.83	0.53	0.60	1.33	0.95–1.84
32–36 weeks	0.48	0.77	2.07	1.74–2.46	0.23	0.77	0.99	0.54–1.81
Fetal (Salomon)								
All preterm	0.53	0.77	2.38	2.15–2.63	0.30	0.78	1.33	1.03–1.72
<28 weeks	0.52	0.77	2.20	1.85–2.61	0.25	0.82	1.40	0.84–2.32
28–31 weeks	0.61	0.77	2.66	2.28–3.09	0.50	0.58	1.20	0.85–1.69
32–36 weeks	0.49	0.79	2.40	2.03–2.83	0.20	0.79	0.97	0.50–1.89

Se, Sensitivity; Sp, Specificity; LR, Likelihood Ratio.

© 2013 RCOG

Discussion

Main findings

In this study, we found that a subpopulation-based birthweight standard, obtained from a population from which births affected by maternal diseases were excluded, could identify preterm infants at a significantly increased risk of stillbirth and in-hospital death, who were missed by a 'conventional' population-based birthweight standard. The use of fetal standards increased the proportion of infants who (i) were identified as SGA but (ii) had no increased risk of poor perinatal outcomes.

Strengths and weaknesses

Questions regarding the validity of the birthweight as a reference standard for the estimation of fetal growth emerged because preterm birth was increasingly recognised as an event linked to abnormal fetal growth patterns. Indeed, there is evidence that preterm births are frequently growth restricted,[3,20] even in the case of spontaneous onset of labour,[21,22] when intrauterine growth restriction is assessed using a fetal weight standard. To address this limitation, we have recently proposed a new birthweight standard, based on the subpopulation of newborns that excludes births to mothers diagnosed with gestational or chronic maternal diseases, which could affect the weight of the fetus.[5] We recognise that, in contrast to fetal weight standards, our approach could not be used to assess the actual growth velocity of preterm newborns as birthweight standards are based on cross-sectional measures. However, the results of our study suggest that the subpopulation-based birthweight standard provides an acceptably accurate 'proxy' for the diagnosis of insufficient fetal growth.

Our study was limited to preterm newborns. Indeed, as our study was conducted on a French population, we wanted to validate our standard with both the US fetal standard,[13] which is largely used worldwide, and the only French fetal standard.[14] Unfortunately, the Salomon et al. standard is limited to preterm fetuses up to 36 weeks of gestation. However, the findings were similar when we compared the performance of our subpopulation-based birthweight standard with the US fetal standard[13] for term newborns (data not shown). Another limitation was that our study had a limited size, nevertheless the rates of stillbirths and in-hospital deaths found in our sample of newborns <37 weeks of gestation, are generally consistent with recently reported rates in a national Swedish cohort[23] and a national Scottish cohort.[18] Moreover, because of the small number of stillbirths and in-hospital deaths in our study population, some non-significant results in gestational age-stratified analyses may reflect insufficient statistical power. Therefore, further studies of larger samples are necessary to compare the predictive ability of fetal versus subpopulation-based birthweight standards.

Interpretation

We found that preterm newborns with birthweight above the 10th centile of our novel subpopulation-based birthweight standard[5] but below the 10th centile of the fetal standards had no increase in the risk of poor perinatal prognosis compared with non-SGA newborns above the 10th centile of the fetal standards. In this study, we compared our subpopulation-based birthweight standards with fetal standards,[13,14] in which fetal weights were estimated from ultrasonic measurements of fetal parts, based on the equation proposed by Hadlock et al.[9] Several previous studies showed that preterm infants are somewhat smaller than the fetuses of the same gestational age who are still *in utero*.[3,20–22] These discrepancies have been related to gestational hypertensive diseases, pre-eclampsia and other maternal conditions that promote both intrauterine growth restriction and preterm birth (spontaneous or induced). However, our results indicate that the difference between fetal and neonatal weight standards persists even when the main gestational diseases affecting fetal growth are excluded. This observation favours the hypothesis that fetal ultrasound may overestimate fetal weights before 37 weeks of gestation. Indeed, the overestimation of fetal weight by ultrasound measurement has been already reported in previous studies.[24,25] Such potential overestimation of fetal weight by ultrasound method would result in the centiles based on the fetal standards being too high and, therefore might lead to misclassifying as SGA some newborns who in reality are not SGA. This hypothesis could explain why we found that the group of newborns classified as SGA by the fetal standards only, but not by the subpopulation-based birthweight standard, had no increase in the risk of poor perinatal outcomes.

It has also been suggested that the use of sex-specific antenatal standards may improve the prenatal assessment of fetal growth,[26] because non-sex-specific growth curves tend to overestimate the weight of females and underestimate the weight of males. Yet, in our analyses, the non sex-specific US fetal weight standard,[13] and the sex-specific French fetal weight standard[14] performed very similarly in terms of identifying newborns at increased risks of poor perinatal outcomes.

Even if the proposed subpopulation-based birthweight standard improved prediction of perinatal deaths and stillbirths for infants born before 37 weeks of gestation, our results revealed that the SGA groups identified by all fetal weight and birthweight standards considered had low sensitivities and likelihood ratios (Table 3). These results are consistent with previous published studies.[19,23] This confirms that fetal and neonatal weight standards alone are

© 2013 RCOG

not sufficient to accurately predict poor perinatal outcomes for individual newborns. Whereas a well-designed standard can identify subgroups with statistically significantly and clinically importantly risk increases, additional clinical and fetal investigations are necessary to enhance the prognosis for individual infants. For instance, umbilical artery Doppler velocimetry has become a clinical standard for identifying early-onset fetal growth restriction, and its use has led to reductions in perinatal death.[27]

Conclusion

We found that, in a French population of preterm newborns, a revised birthweight standard, based on a subpopulation from which births affected by maternal diseases were excluded, improved the identification of newborns at an increased risk of poor perinatal prognosis, compared with fetal weight standards.

This approach might provide a new simple tool, to be used in clinical practice, in combination with other monitoring parameters employed during pregnancy, to help identify infants with intrauterine growth restriction, who are at an increased risk of stillbirths and in-hospital deaths.

Disclosure of interests

None.

Contribution to authorship

CF was the leader of the statistical analysis, and contributed to writing of the paper and interpretation of the results. CQ, MA and JBG contributed to drafting the paper and interpretation of the results. AB and PS contributed to drafting the paper.

Details of ethics approval

This study was approved by the French commission for data protection (Commission Nationale de l'Informatique et des Libertés—CNIL—Paris. France). Request number # 98003718.

Funding

Funding was received from URCAM and ARH of Burgundy, FICQSV.

Acknowledgements

We thank all the neonatologists, obstetricians, midwives and members of the neonatal networks who participated in the study: Centre Hospitalier Universitaire de Dijon, centres hospitaliers généraux de Beaune, Châtillon sur Seine, Chalon sur Saône, Mâcon, Paray le Monial, Montceau les Mines, Le Creusot, Autun, Chenôve, Semur en Auxois, Clamecy, Nevers, Decize, Auxerre, Sens, Clinique Sainte-Marthe (Dijon), Clinique Cosne sur Loire and Clinique Auxerre. Michal Abrahamowicz is a James McGill Professor of Biostatistics at McGill University. ■

References

1 Ancel PY, Marret S, Larroque B, Arnaud C, Zupan-Simunek V, Voyer M, et al. Are maternal hypertension and small-for-gestational age risk factors for severe intraventricular hemorrhage and cystic periventricular leukomalacia? Results of the EPIPAGE cohort study. *Am J Obstet Gynecol* 2005;193:178–84.

2 Steer P. The epidemiology of preterm labour. *BJOG* 2005;112(Suppl. 1):1–3.

3 Ott WJ. Intrauterine growth retardation and preterm delivery. *Am J Obstet Gynecol* 1993;168:1710–5; discussion 5–7.

4 Reeves S, Bernstein IM. Optimal growth modeling. *Semin Perinatol* 2008;32:148–53.

5 Ferdynus C, Quantin C, Abrahamowicz M, Platt R, Burguet A, Sagot P, et al. Can birth weight standards based on healthy populations improve the identification of small-for-gestational-age newborns at risk of adverse neonatal outcomes? *Pediatrics* 2009;123:723–30.

6 Zaw W, Gagnon R, da Silva O. The risks of adverse neonatal outcome among preterm small for gestational age infants according to neonatal versus fetal growth standards. *Pediatrics* 2003;111: 1273–7.

7 Cooke RW. Conventional birth weight standards obscure fetal growth restriction in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2007;92:F189–92.

8 Ehrenkranz RA. Estimated fetal weights versus birth weights: should the reference intrauterine growth curves based on birth weights be retired? *Arch Dis Child Fetal Neonatal Ed* 2007;92:F161–2.

9 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.

10 Cornet B, Gouyon JB, Binquet C, Sagot P, Ferdynus C, Metral P, et al. Evaluation regionale en perinatalite: mise en place d'un recueil continu d'indicateurs [Using discharge abstracts as a tool to assess a regional perinatal network]. *Rev Epidemiol Sante Publique* 2001;49:583–93.

11 Quantin C, Gouyon B, Avillach P, Ferdynus C, Sagot P, Gouyon JB. Using discharge abstracts to evaluate a regional perinatal network: assessment of the linkage procedure of anonymous data. *Int J Telemed Appl* 2009;2009:181842.

12 Blondel B, Supernant K, Du Mazaubrun C, Breart G, Enquête nationale périnatale. 2003 [www.sante.gouv.fr/htm/dossiers/perinat03/sommaire.htm]. Accessed 05 june 2012.

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

14 Salomon LJ, Bernard JP, Ville Y. Estimation of fetal weight: reference range at 20–36 weeks' gestation and comparison with actual birth-weight reference range. *Ultrasound Obstet Gynecol* 2007;29:550–5.

15 Yudkin PL, Wood L, Redman CW. Risk of unexplained stillbirth at different gestational ages. *Lancet* 1987;1:1192–4.

16 Joseph KS. Incidence-based measures of birth, growth restriction, and death can free perinatal epidemiology from erroneous concepts of risk. *J Clin Epidemiol* 2004;57:889–97.

17 Khan KS, Bakour SH, Bossuyt PM. Evidence-based obstetric and gynaecologic diagnosis: the STARD checklist for authors, peer-reviewers and readers of test accuracy studies. *BJOG* 2004;111: 638–40.

© 2013 RCOG

18 Hemming K, Bonellie S, Hutton JL. Fetal growth and birthweight standards as screening tools: methods for evaluating performance. *BJOG* 2011;118:1477–83.

19 Zhang J, Mikolajczyk R, Grewal J, Neta G, Klebanoff M. Prenatal application of the individualized fetal growth reference. *Am J Epidemiol* 2011;173:539–43.

20 Lackman F, Capewell V, Richardson B. daSilva O, Gagnon R. The risks of spontaneous preterm delivery and perinatal mortality in relation to size at birth according to fetal versus neonatal growth standards. *Am J Obstet Gynecol* 2001;184:946–53.

21 Morken NH, Kallen K, Jacobsson B. Fetal growth and onset of delivery: a nationwide population-based study of preterm infants. *Am J Obstet Gynecol* 2006;195:154–61.

22 Hediger ML, Scholl TO, Schall JI, Miller LW, Fischer RL. Fetal growth and the etiology of preterm delivery. *Obstet Gynecol* 1995;85: 175–82.

23 Hemming K, Hutton JL, Bonellie S. A comparison of customized and population-based birth-weight standards: the influence of gestational age. *Eur J Obstet Gynecol Reprod Biol* 2009;146:41–5.

24 Dudley NJ. A systematic review of the ultrasound estimation of fetal weight. *Ultrasound Obstet Gynecol* 2005;25:80–9.

25 Abele H, Hoopmann M, Wagner N, Hahn M, Wallwiener D, Kagan KO. Accuracy of sonographic fetal weight estimation of fetuses with a birth weight of 1500 g or less. *Eur J Obstet Gynecol Reprod Biol* 2010;153:131–7.

26 Schwarzler P, Bland JM, Holden D, Campbell S, Ville Y. Sex-specific antenatal reference growth charts for uncomplicated singleton pregnancies at 15–40 weeks of gestation. *Ultrasound Obstet Gynecol* 2004;23:23–9.

27 Maulik D, Mundy D, Heitmann E. Evidence-based approach to umbilical artery Doppler fetal surveillance in high-risk pregnancies: an update. *Clin Obstet Gynecol* 2010;53:869–78.

Commentary on 'Which chart should be used to assess fetal growth? What if the best answer is "none of the above"?'

The most appropriate weight-for-age chart for assessing fetal growth remains controversial. Options include charts based on birthweights, estimated fetal weights and birthweights 'customised' to account for maternal characteristics. In this study, Ferdynus et al. (*BJOG* 2013;DOI: 10.1111/1471-0528.12282) add to the debate by evaluating a new option, a chart based on birthweights of newborns delivered to women without comorbid conditions linked to fetal growth restriction.

Birthweight standards (in which weight centiles are based only on weights of 'healthy' infants) have been argued to have greater clinical utility than birthweight references (in which weight centiles are based on weights of all births in a population) because they compare an infant's weight with that of normally grown infants, rather than merely establishing the infant's size relative to that of others in the population (Zhang et al. *AJOG* 2010;202:522–8). Weight-for-age standards (rather than references) are also well accepted for the assessment of paediatric growth, where charts such as the World Health Organization Child Growth Standards are derived from the weights of term births exclusively or predominantly breastfed until at least 4 months with no known constraints on growth and free of significant morbidity (deOnis et al. *Food Nutr Bull* 2004;25:S15–26). The chart of Ferdynus et al., which excludes pregnancies complicated by maternal conditions related to fetal growth restriction, should therefore theoretically be a better tool for identifying growth-restricted preterm infants. The study's finding that births classified as small-for-gestational-age by the new chart alone had relative risks of stillbirth and in-hospital death of 2.6 and 2.8, respectively, appears to support its value. However, several points deserve consideration before advocating the chart's use in clinical practice.

First, identifying which pregnancies were complicated by conditions that affect fetal growth is not straightforward. It is challenging to describe any delivery at very preterm ages as 'healthy', and it seems plausible that factors other than documented maternal comorbidities may also be causes of poor growth and preterm birth. Large sample sizes are needed to create weight-for-age charts, but large databases often lack the accuracy and degree of clinical detail needed to correctly identify pregnancies with compromised fetal growth. Rather than attempting to define and identify such pregnancies, it may be better to establish thresholds for 'high risk' based on the weight or weight centile of population birthweights at each gestational age, where risks of adverse outcomes become increased (instead of trying to identify a population or subpopulation in which risks become increased at the 10th centile (Boulet et al. *AJOG* 2006;195:1571–7).

Second, evaluating whether a new chart is 'better' by examining only relative risks of small-for-gestational-age has limitations. An important contribution of this study is that the authors additionally evaluated whether the new chart was 'better' using commonly accepted approaches for evaluating diagnostic and predictive tools: sensitivity, specificity and likelihood ratios. The results of these analyses helped to highlight an important point that may not otherwise be readily apparent: while the new chart may be 'better' than population birthweight or estimated fetal weight charts, it is still not particularly good. The likelihood ratios for all charts were < 5, suggesting that, irrespective of their various refinements, weight-for-age charts are poor diagnostic tools when evaluated by standard criteria (where likelihood ratios between 5 and 10 would provide moderate evidence to rule in intrauterine growth restriction, and likelihood ratios >10 would provide

© 2013 RCOG

strong evidence). This confirms the importance of developing altogether new approaches for assessing fetal growth, such as ones that integrate weight-for-age with ultrasound and placental data (Zhang et al. *AJOG* 2010;202:522–8).

Acknowledgements

JAH is supported by New Investigator awards from the Canadian Institutes of Health Research and the Michael Smith Foundation for Health Research

Disclosure of interest

The author has no interests to disclose. ■

J Hutcheon

Department of Obstetrics & Gynaecology, University of British Columbia, Vancouver, BC, Canada

© 2013 RCOG