Improving Antenatal Prediction of Small-for-Gestational-Age Neonates by Using Customized Versus Population-Based Reference Standards

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Objectives—The purpose of this study was to evaluate whether the use of customized fetal reference standards improves the prenatal detection of intrauterine growth restriction.

Methods—We conducted a retrospective cohort study. Singleton pregnancies with a diagnosis of a small-for-gestational-age (SGA) fetus based on the in utero reference standard of Hadlock et al (*Am J Obstet Gynecol* 1985; 151:333–337; *Radiology* 1991; 181:129–133) were identified from our ultrasound database, and customized percentiles were calculated by adjusting for maternal height, weight, ethnicity, parity, and sex.

Results—A total of 300 pregnancies were identified as SGA by both the Hadlock and customized standards, and 60 were identified as SGA by the Hadlock standard only. Small-for-gestational age pregnancies identified by the Hadlock standard only were significantly less likely to have any abnormal sonographic findings, including an elevated head to abdominal circumference ratio (8.3% versus 21.7%; $P = .019$), oligohydramnios (3.3% versus 13%; $P = .027$), abnormal umbilical artery Doppler findings (3.4% versus 14.7%; $P = .017$), maternal hypertensive disease (3.3% versus 12.7%; $P = .041$), and preterm delivery (6.7% versus 27.7%; $P < .001$). There was no difference in neonatal intensive care unit admission rates; however, neonates identified as SGA by the Hadlock standard only were less likely to have a postnatal diagnosis of SGA (9.1% versus 78.3%; $P < .001$) and had a shorter neonatal intensive care unit stay (median, 2 versus 8 days; $P < .001$).

Conclusions—Using a customized standard, we have identified a population of pregnancies with low rates of antenatal complications and sonographic findings associated with pathologic growth. Adoption of customized standards to improve our antenatal detection rate of intrauterine growth restriction may decrease the need for intervention in healthy but constitutionally small fetuses.

Key Words—customized growth standards; fetal growth; intrauterine growth restriction; small-for-gestational-age; umbilical artery Doppler sonography

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Abbreviations

GA, gestational age; IUGR, intrauterine growth restriction; NICU, neonatal intensive care unit; SGA, small-for-gestational-age

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Intrauterine growth restriction (IUGR) is associated with poor perinatal outcomes and long-term morbidity. Antenatal detection using standardized fetal growth curves is limited by the difficulty in distinguishing IUGR from healthy but constitutionally small fetuses. Additional sonographic findings that are associated with IUGR include oligohydramnios, asymmetric growth (abnormal head to abdominal circumference ratio), and abnormal umbilical artery Doppler velocimetric find-

ings.[1,2] However, these findings are not useful in screening for IUGR, as growth restriction may occur in their absence.[3–5] The accuracy of prenatal diagnosis of IUGR may be improved by application of customized size standards,[6] which take into account physiologic determinants of fetal growth, including maternal height, weight, parity, ethnicity, and fetal sex, and may be preferred over population size standards in assessment for IUGR. Locally derived standards have been published for several countries, and the use of customized growth curves has been recommended by the Royal College of Obstetricians and Gynaecologists guidelines for management of the small-for-gestational-age (SGA) fetus.[7,8]

Gardosi and Francis[9] validated population-based customized growth coefficients for a US population using a large prospective cohort of more than 35,000 pregnancies. They demonstrated superior detection of adverse pregnancy outcomes, including hypertensive disease, antepartum hemorrhage, stillbirth, and neonatal death, using customized birth weight percentiles.[10] In contrast, pregnancies defined as SGA by population but not by customized percentiles were not at increased risk for adverse pregnancy outcomes. Bukowski et al[11] and Odibo et al[12] also evaluated customized fetal standards in US populations and noted improved detection of pregnancies at risk for adverse outcomes.

Not all studies have demonstrated superiority of customized standards in predicting adverse outcomes. In a large US retrospective cohort, Larkin et al[13] demonstrated that after adjusting for gestational age (GA) at delivery, there was no difference in neonatal outcomes between SGA by population versus SGA by a customized standard; however, the risk of hypertensive disorders of pregnancy remained increased in the pregnancies identified as SGA by the customized standard. Hutcheon et al[14] compared the predictive value of using birth weight standards, intrauterine standards, and customized birth weight standards in a large Swedish birth registry. Relative risks of stillbirth and early neonatal mortality among SGA births were similar in the intrauterine standard and customized standard groups, and they concluded that customization does not significantly improve prediction of perinatal mortality. The benefits of customized standards may be largely derived from their use of the in utero standard of Hadlock et al,[15,16] as this reference is not biased and is superior to birth weight references in identifying perinatal abnormalities.

Our objective was to determine whether customized fetal size standards improve antenatal detection of IUGR over the Hadlock standard in a US population by comparing associated pathologic sonographic findings of an elevated head to abdominal circumference ratio, oligohydramnios, abnormal umbilical artery Doppler findings, maternal risk factors (hypertensive disease and diabetes), and delivery outcomes (preterm delivery, induction and cesarean delivery rates, and neonatal intensive care unit [NICU] admission).

Materials and Methods

We conducted a retrospective cohort study at a single academic center. Singleton pregnancies with a GA of 32 weeks or later and a diagnosis of an SGA fetus, defined as estimated fetal weight below the 10th percentile based on the Hadlock in utero reference standard[15,16] were identified from our ultrasound database between January 2006 and July 2010. Exclusion criteria were major congenital anomalies, poor dating (first sonographic examination at >20 weeks), missing maternal demographic information, and delivery at a different institution. The study was approved by the Institutional Review Board of Weill Cornell Medical College.

Gestational age was determined on the basis of the first day of the last menstrual period or date of conception and confirmed by sonography before 20 weeks. Sonographic dating was used when the last menstrual period was uncertain or when there was a difference of greater than 5 days from the last menstrual period to first-trimester sonography. Most cases were dated by a last menstrual period that was consistent with first-trimester sonography. Cases with poor dating (no sonographic examination at <20 weeks) were excluded.

Customized percentiles for all estimated fetal weights were calculated using the GROW customized percentile calculator for the United States according to a previously described method by adjusting for constitutional variables, including maternal height, weight at the first prenatal visit (booking weight), ethnicity (African American, European, Hispanic, or other), parity, and fetal sex. The calculator has been previously validated for use in US populations,[9] and the software is available at www.gestation.net.[17] Pregnancies were identified as SGA by both the Hadlock standard and the customized standard or by the Hadlock standard only. Most pregnancies had a single estimated fetal weight measurement after 32 weeks. For pregnancies with serial sonographic measurements, only the last estimated fetal weight before delivery was used for calculation of percentiles.

Oligohydramnios was defined as an amniotic fluid index of less than 5. An elevated head to abdominal circumference ratio was defined as a measurement above the 95th percentile for GA.[18] Abnormal umbilical artery

Doppler findings were defined as either a systolic to diastolic ratio above the 95th percentile for GA or absent or reversed diastolic flow. Postnatal diagnosis of SGA was based on an assessment by a neonatologist and documented in the hospital discharge summary. The neonatologist used a customized birth weight standard to define postnatal SGA. The customized birth weight standard is based on locally derived birth weights and adjusted for sex and ethnicity (Caucasian, African American, Hispanic, or other).

Statistical comparisons were performed using Mann-Whitney *U* and Student *t* tests for continuous variables and Fisher exact and χ^2 tests for categorical variables. Multivariate logistic regression was used to adjust for GA in the postnatal diagnosis of IUGR, using a main-effects model and list-wise deletion of missing data. All analyses were performed with SPSS software (versions 19 and 20; SPSS Inc, Chicago, IL).

Results

A total of 360 pregnancies meeting inclusion and exclusion criteria were identified as SGA by the Hadlock standard. Sixty pregnancies (16.7%) were identified as SGA by the Hadlock standard only but not classified as SGA when evaluated by the customized standard, and 300 pregnancies (83.3%) were identified as SGA by both the Hadlock and customized standards. The median GA at the time of sonography was 36.6 weeks (range, 32.0–40.4 weeks), and the median GA at the time of delivery was 37.6 weeks (range, 32.0–41.6 weeks). Maternal demographic factors used to calculate the customized growth percentiles are listed in Table 1. Mothers of SGA neonates identified by the Hadlock standard only were shorter, weighed less, and were more likely to be primiparous and of non-European ethnicity; SGA neonates identified by the Hadlock standard only were more likely to be female.

Pregnancy outcomes and prenatal risk factors for IUGR are listed in Table 2. Pregnancies identified as SGA by the Hadlock standard only were significantly less likely to have any abnormal sonographic findings, including an elevated head to abdominal circumference ratio (8.3% versus 21.7%; $P = .019$), oligohydramnios (3.3% versus 13%; $P = .027$), and abnormal umbilical artery Doppler findings (3.4% versus 14.7%; $P = .017$). Mothers of SGA infants identified by the Hadlock standard only were significantly less likely to have hypertensive disease, including chronic hypertension, gestational hypertension, and preeclampsia (3.3% versus 12.7%; $P = .041$). Lower labor induction rates were noted in SGA pregnancies identified by the Hadlock standard only (38.3% versus 63.0%; $P < .001$). However, there was no statistical difference in overall cesarean delivery rates and cesarean delivery rates for a nonreassuring fetal status between pregnancies classified as SGA by the

Table 1. Demographic Factors and SGA

Factor	Total	SGA (Hadlock and Customized Standards)	SGA (Hadlock Standard Only)	*P*
	360	300	60	
Maternal age, y	31.8 ± 5.6	31.9 ± 5.6	31.5 ± 5.5	.588[b]
Primiparous[a]	231 (64.0)	179 (60.0)	52 (87.0)	<.001[c]
Height, cm[a]	161.4 ± 7.0	162.0 ± 7.2	158.3 ± 5.5	<.001[b]
Booking weight, kg[a]	59.9 ± 13.3	61.3 ± 13.6	52.4 ± 8.5	<.001[b]
Body mass index, kg/m^2	23.0 ± 4.8	23.1 ± 4.7	22.4 ± 5.5	.296[b]
Ethnicity[a]				
African American	30 (8.3)	26 (8.7)	4 (6.7)	<.001[d]
European	186 (51.7)	168 (56.0)	18 (30.0)	
Hispanic	38 (10.6)	35 (11.7)	3 (5.0)	
Other	106 (29.4)	71 (23.7)	35 (58.3)	
GA at sonography, wk[a]	36.6 (36.0–37.6)	36.5 (35.6–37.5)	37.3 (36.2–38.2)	.073[e]
Female fetus[a]	202 (56.0)	156 (52.0)	46 (77.0)	<.001[c]
Estimated fetal weight, g[a]	2239 ± 337	2193 ± 342	2467 ± 187	<.001[b]

Data are presented as mean ± SD, number (percent), and median (interquartile range).
[a] Factors used to calculate customized growth curves.
[b] Student *t* test.
[c] Fisher exact test.
[d] χ^2 test.
[e] Mann-Whitney *U* test.

Table 2. Risk Factors and Pregnancy Outcomes

Risk Factor/Outcome	Total	SGA (Hadlock and Customized Standards)	SGA (Hadlock Standard Only)	*P*
	360	300	60	
Sonographic findings				
Elevated head/abdominal circumference ratio	70 (19.4)	65 (21.7)	5 (8.3)	.019[b]
Oligohydramnios	41 (11.4)	39 (13.0)	2 (3.3)	.027[b]
Abnormal umbilical artery Doppler findings[a]	45/350 (12.9)	43/292 (14.7)	2/58 (3.4)	.017[b]
Hypertensive disease	40 (11.1)	38 (12.7)	2 (3.3)	.041[b]
Diabetes	23 (6.3)	20 (6.7)	3 (5.0)	.779[b]
Induction rate	212 (58.9)	189 (63.0)	23 (38.3)	<.001[b]
Cesarean delivery	137 (38.1)	115 (38.3)	22 (36.7)	.885[b]
Cesarean delivery for nonreassuring fetal status	33/137 (24.0)	28/115 (24.3)	5/22 (22.7)	>.99[b]
GA at delivery, wk	37.6 (32.0–41.6)	37.4 (32.0–41.3)	39.0 (35.5–41.6)	<.001[c]
Preterm delivery (<37 wk)	87 (24.2)	83 (27.7)	4 (6.7)	<.001[b]
NICU admission	77 (21.4)	66 (22.0)	11 (18.3)	.607[b]
Apgar scores (5 min)	9 (5–10)	9 (6–10)	9 (5–9)	.398[c]
Birth weight, g	2441 ± 409	2387 ± 408	2711 ± 295	<.001[d]

Data are presented as number (percent), median (range), and mean ± SD.
[a] Ten cases with no umbilical artery Doppler evaluations were excluded.
[b] Fisher exact test.
[c] Mann-Whitney *U* test.
[d] Student *t* test.

Hadlock standard only and by both the Hadlock and customized standards (Table 2). Neonates classified as SGA by the Hadlock standard only were delivered at a later gestation (median, 39.0 versus 37.4 weeks; $P < .001$) and had a larger mean birth weight (mean ± SD, 2711 ± 295 versus 2387 ± 408 g; $P < .001$) compared with those classified as SGA by both the Hadlock and customized standards.

A total of 77 neonates (21.4%) were admitted to the NICU, and there was no difference observed in median 5-minute Apgar scores or frequency of NICU admission between the groups (NICU admission rates of 18.3% for SGA by the Hadlock standard only versus 22.0% for SGA by both the Hadlock and customized standards; $P = .607$; Table 2). Neonatal intensive care unit admission data, including birth weight, GA, length of stay, and diagnosis, are listed in Table 3. Infants who were identified as SGA by the Hadlock standard only had a significantly shorter NICU stay (median, 2 versus 8 days; $P < .001$) and were significantly less likely to have a postnatal diagnosis of SGA compared with those identified as SGA by both the Hadlock and customized standards (9.1% versus 78.3%; $P < .001$). Postnatal diagnosis of SGA remained significant after adjusting for GA at delivery using multivariate logistic regression ($P = .015$; odds ratio, 0.062; confidence interval, 0.007–0.588).

Table 3. Neonatal Intensive Care Unit Data

Factor	Total	SGA (Hadlock and Customized Standards)	SGA (Hadlock Standard Only)	*P*
	77 (21.4)	66 (22.0)	11 (18.3)	
NICU birth weight, g	2025 ± 482	1918 ± 415	2672 ± 335	<.001[b]
NICU GA, wk	36.3 (35.1–37.5)	36.1 (34.6–37.3)	38.2 (37.3–40.1)	<.001[c]
NICU length of stay, d[a]	6 (4–13)	8 (5–14)	2 (2–4)	<.001[c]
NICU diagnosis of SGA[a]	48/71 (67.6)	47/60 (78.3)	1/11 (9.1)	<.001[d]

Data are presented as number (percent), mean ± SD, and median (interquartile range).
[a] Six cases with missing information on NICU length of stay and diagnosis and were excluded.
[b] Student *t* test.
[c] Mann-Whitney *U* test.
[d] Fisher exact test.

Discussion

In this study, pregnancies identified as SGA by the Hadlock standard but not by the customized standard were significantly less likely to have additional sonographic findings suggestive of pathologic growth, including oligohydramnios, an abnormal head to abdominal circumference ratio, and abnormal umbilical artery Doppler findings. This group had lower antenatal complications, including lower rates of maternal hypertensive disease, labor induction, and preterm delivery. Neonates identified as SGA by the Hadlock standard only were more likely to be female, and the mothers were shorter, lighter, and more likely to be primiparous and of non-European ethnicity. These characteristics are suggestive of constitutional SGA and not pathologic IUGR. Although NICU admission rates were not statistically different between the groups, the NICU length of stay was significantly shorter in the group identified as SGA by the Hadlock standard only, and this group was less likely to have a postnatal diagnosis of SGA.

A limitation of this study was that we did not include pregnancies that were identified as SGA by the customized standard only but not by the Hadlock standard. Our study design limited inclusion in this way because our ultrasound database does not routinely calculate customized growth, and capturing these cases would not have been feasible. In addition, we would not have had umbilical artery Doppler studies for comparison, as these are not routinely performed on non-SGA fetuses. In a large US cohort, Gardosi and Francis[10] identified 17.4% of neonates as SGA by a population standard but not by a customized standard (similar to our rate of 16.7%) and an additional 32.7% of neonates as SGA by the customized standard but not by the population standard.[10] Consistent with our findings, pregnancies identified as SGA by the population standard only were not at increased risk for adverse outcomes. In contrast, pregnancies identified as SGA by the customized standard only had the highest risk of adverse outcomes, including stillbirth and neonatal death. This finding may be related to the fact that these pregnancies were less likely to be identified, and strategies to prevent poor outcomes were not implemented.

Most studies examining the application of customized growth standards compare pregnancy outcomes using birth weight. Very few studies have examined the use of estimated fetal weight and sonographic findings in the antenatal application of customized growth standards, mainly because this information is often unavailable in large databases. McCowan et al[19] evaluated birth weight, Doppler studies, and pregnancy outcomes in a New Zealand cohort of 374 SGA pregnancies suspected antenatally. They noted low rates of abnormal Doppler findings, cesarean deliveries for fetal distress, and neonatal morbidity in the group identified as SGA by a population parameter only (n = 32) compared with groups identified as SGA by a customized parameter only and by both the customized and population parameters, and they concluded that these neonates are likely to be constitutionally small and not growth restricted. Although the low rate of Doppler abnormalities in the group identified as SGA by the population standard supports the exclusion of IUGR in this group, normal Doppler findings in the group identified as SGA by the customized standard do not exclude IUGR. Figueras et al[20] demonstrated that in their cohort of 369 SGA neonates identified by customized birth weight standards, 81% had normal Doppler indices but were still noted to have an elevated risk of neonatal morbidity compared with non-SGA neonates.

Although in clinical practice, the 10th percentile cutoff is often used for prenatal identification of SGA, the optimal cutoff for predicting adverse outcomes among SGA fetuses with normal sonographic findings is not well established. Zhang et al[21] compared a standard sonographic reference for estimated fetal weight versus an individual (customized) reference at both the 5th and 10th percentiles for predicting adverse perinatal outcomes. They noted that the incidence of adverse outcomes increased only after the estimated fetal weight fell below the 5th percentile by either reference and that this percentile may be a better cutoff point for defining SGA.[21] The study population was homogeneous and predominantly white, however, thus limiting conclusions on possible benefits of individual growth references. Savchev et al[22] demonstrated that in a term cohort of SGA fetuses with normal placental and cerebral Doppler findings, only those with an estimated fetal weight below the 3rd percentile (based on local customized standards) were at higher risk for adverse perinatal outcomes.

Our study included a diverse ethnic population, but dividing it into only 4 ethnic categories (European, African American, Hispanic, and other) may have limited customization accuracy for individuals because 29.4% of our population was classified as other, which represented a heterogeneous group including Asian, Pacific Islander, Native American, and multiethnic women. In a large World Health Organization global survey cohort, Mikolajczyk et al[23] demonstrated that adjustment for the country of origin alone (by adjusting the mean birth weight at 40 weeks for local populations from 24 world countries) significantly improved prediction of adverse perinatal out-

comes for SGA compared with a noncustomized fetal weight reference. Several studies outside the United States have noted significant birth weight variation in Asian populations compared with European populations.[24,25] However, US cohorts have been limited by small numbers of Asian women, and additional validation of customized growth curves for Asian American women is needed.

In pregnancies identified as SGA based on the Hadlock in utero reference standard, the use of a customized reference standard improves the antenatal detection of IUGR by identifying a subpopulation with constitutionally small fetuses and low rates of sonographic findings associated with pathologic growth, antenatal complications, and a postnatal diagnosis of an SGA neonate. Prospective studies are needed to evaluate the application of customized reference standards for detection of IUGR in the US population.

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