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OBSTETRICS

Dichorionic twin trajectories: the NICHD Fetal Growth Studies

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BACKGROUND: Systematic evaluation and estimation of growth trajectories in twins require ultrasound measurements across gestation that are performed in controlled clinical settings. Currently, there are few such data for contemporary populations. There is also controversy about whether twin fetal growth should be evaluated with the use of the same benchmarks as singleton growth.

OBJECTIVES: Our objective was to define the trajectory of fetal growth in dichorionic twins empirically using longitudinal 2-dimensional ultrasonography and to compare the fetal growth trajectories for dichorionic twins with those based on a growth standard that was developed by our group for singletons.

STUDY DESIGN: A prospective cohort of 171 women with twin gestations was recruited from 8 US sites from 2012—2013. After an initial sonogram at 11 weeks 0 days—13 weeks 6 days of gestation during which dichorionicity was confirmed, women were assigned randomly to 1 of 2 serial ultrasonography schedules. Growth curves and percentiles were estimated with the use of linear mixed models with cubic splines. Percentiles were compared statistically at each gestational week between the twins and 1731 singletons, after adjustment for maternal age, race/ethnicity, height, weight, parity, employment, marital status, insurance, income, education, and infant sex. Linear mixed models were used to test for overall differences between the twin and singleton trajectories with the use of likelihood ratio tests of interaction terms between spline mean structure terms and twin-singleton indicator variables. Singleton standards were weighted to correspond to the distribution of maternal race in twins. For those ultrasound measurements in which there were significant global tests for differences between twins and singletons, we tested for week-specific differences using Wald tests that were computed at each gestational age. In a separate analysis, we evaluated the degree of reclassification in small for gestational age, which was defined as <10th percentile that would be introduced if fetal growth estimation for twins was based on an unweighted singleton standard.

RESULTS: Women underwent a median of 5 ultrasound scans. The 50th percentile abdominal circumference and estimated fetal weight trajectories of twin fetuses diverged significantly beginning at 32 weeks of gestation; biparietal diameter in twins was smaller from 34—36 weeks of gestation. There were no differences in head circumference or femur length. The mean head circumference/abdominal circumference ratio was progressively larger for twins compared with singletons beginning at 33 weeks of gestation, which indicated a comparatively asymmetric growth pattern. At 35 weeks of gestation, the average gestational age at delivery for twins, the estimated fetal weights for the 10th, 50th, and 90th percentiles were 1960, 2376, and 2879 g for dichorionic twins, respectively, and 2180, 2567, and 3022 g for the singletons, respectively. At 32 weeks of gestation, the initial week when the mean estimated fetal weight for twins was smaller than that of singletons, 34% of twins would be classified as small for gestational age with the use of a singleton, non-Hispanic white standard. By 35 weeks of gestation, 38% of twins would be classified as small for gestational age.

CONCLUSION: The comparatively asymmetric growth pattern in twin gestations, initially evident at 32 weeks of gestation, is consistent with the concept that the intrauterine environment becomes constrained in its ability to sustain growth in twin fetuses. Near term, nearly 40% of twins would be classified as small for gestational age based on a singleton growth standard.

Key words: dichorionic, estimated fetal weight, fetal growth, twin

Twin gestations represented 3.4% of US births in 2014.[1] The infant mortality rate is higher for twins vs singletons (23.6 vs 5.4 per 1000 live births) as is the rate of cerebral palsy (7 vs 1.6 per 1000 live births).[2,3] Cross-sectional US natality data demonstrate that, after 28 weeks of gestation, twins are born with lower mean birthweights and that the difference between twins and singletons progressively widens with increasing gestational age, which implies that growth slows at the beginning of the third trimester in twin gestations.[4] However, these findings reflect birth size and do not convey the longitudinal pattern of in utero fetal growth from early in pregnancy. Such cross-sectional studies based on birthweight cannot assess early onset growth abnormalities adequately because the data are biased inherently by preterm deliveries that are associated with complications that may also affect fetal growth or by iatrogenic preterm deliveries that result from suspected growth restriction.

Systematic evaluation and estimation of growth trajectories in twins require ultrasound measurements across gestation. Currently, there are few such data for contemporary populations.[5,6] Furthermore, no previous study of twins that has been performed in multiple clinical centers with a rigorous design that has included training of

EDITORS' CHOICE

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TABLE 1
Maternal characteristics at enrollment by number of fetuses and pregnancy characteristics (n = 171; NICHD Fetal Growth Studies: Twins)

Maternal characteristic	Measure
Race/ethnicity, n (%)	
White/non-Hispanic	93 (54.5)
Black/non-Hispanic	36 (21.1)
Hispanic	33 (19.3)
Asian	8 (4.7)
Multiracial	1 (0.6)
Age, y[a]	31.6 ± 6.1
Gravidity, n (%)	
1	51 (29.8)
2	59 (34.5)
≥3	32 (18.7)
Parity, n (%)	
0	96 (56.1)
1	54 (31.6)
≥2	21 (12.3)
Maternal height, cm[a]	165.1 ± 6.4
Prepregnancy weight, self-reported, kg[a]	75.4 ± 20.2
Prepregnancy body mass index (kg/m^2), n (%)	
<25.0	67 (39.2)
25.0–29.9	39 (22.8)
≥30.0	65 (38.0)
Mean ± SD	28.6 ± 7.0
Marital status, n (%)	
Never married	32 (18.7)
Married/living as married	135 (78.9)
Divorced/separated/widowed	4 (2.3)
Education, n (%)	
<High school	12 (7.0)
High school	22 (12.9)
Some college	29 (17.0)
College undergraduate	70 (40.9)
Postgraduate college	38 (22.2)
Family income, n (%)	
≤$29,999	35 (20.5)
$30,000–49,999	9 (5.3)
$50,000–74,999	14 (8.2)
$75,000–99,999	18 (10.5)
≥$100,000	79 (46.2)

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sonographers, standardization of ultrasound measurements, and assessment of quality control has been conducted.

Understanding fetal growth in twin gestations is important, given that fetal growth is an influential determinant of health and disease in the perinatal period, childhood, and adult life and that there is uncertainty about whether twin fetal growth should be evaluated similarly to singleton growth.[7] Therefore, in collaboration with 8 institutions, the *Eunice Kennedy Shriver* National Institute for Child Health and Human Development (NICHD), National Institutes of Health conducted a prospective cohort study of dichorionic twin gestations as a part of the NICHD Fetal Growth Studies. Our objective was to define empirically the predominant trajectory of fetal growth in dichorionic twins using longitudinal 2-dimensional ultrasonography and to compare and contrast the fetal growth trajectories for dichorionic twins with the singleton growth standard that was previously developed by our group.[8]

Materials and Methods

A prospective cohort study was conducted in which women with dichorionic twin gestations, irrespective of the mode of conception, maternal medical history, or obesity status, were enrolled. Heterogeneity of the population's characteristics in the selection of pregnant women was important to maximize the possibility that factors associated with twin fetal growth could be examined and that the study conclusions would be more generalizable to the population of twins in the United States. Women were enrolled between 8 weeks 0 days and 13 weeks 6 days of gestation. Accurate dating was required for enrollment. Thus, the ultrasound estimate of gestational age had to match the last menstrual period–based gestational age (for the larger twin) according to the following criteria: (1) last menstrual period date and ultrasound date matched within 5 days for gestation estimates between 8 weeks 0 days and 10 weeks 6 days of gestation; (2) 6 days for those between 11 weeks 0 days and 12 weeks 6 days of gestation; and (3) 7 days for those between 13 weeks 0 days and 13 weeks 6 days of gestation. For women with an in vitro fertilization (IVF) conception, a calculated last menstrual period was determined with the date of transfer and embryo age at transfer. Ultrasound determination of chorionicity was established at the initial ultrasound examination. The pregnancy was classified as dichorionic if 2 gestational sacs were present with a thick intervening membrane and twin peak or lambda sign. If chorionicity was unable to be determined, the patient was determined to be ineligible. Chorionicity was confirmed by ultrasound imaging at the subsequent visit. Information on chorionicity was also abstracted from the clinical placenta pathology report.

Inclusion criteria were maternal age 18−45 years and anticipated delivery at the participating hospital. Study participants were excluded if fetal reduction was planned or if the first-trimester sonogram indicated congenital anomalies (structural or chromosomal), increased nuchal translucency (≥3.5 mm) in either twin, monochorionic twins, or crown-rump length discordance >10%, because there is an increased risk of adverse perinatal outcomes with these conditions.[9,10] Recruitment began February 1, 2012, and continued through January 31, 2013, with final data collection completed on September 30, 2014. Institutional Review Board approval was obtained for the NICHD and all participating clinical institutions and the data and imaging coordinating centers.

A standardized ultrasound protocol was developed, and sonographers underwent extensive training and credentialing to ensure high-quality ultrasound images. All study scans were performed on Voluson E8 machines (GE Healthcare, Milwaukee, WI) with standard operating procedures specified. Study data were collected into a customized application of the ViewPoint clinical system (GE Healthcare) with modifications to meet the study goals and electronically uploaded into a web-based data collection system that is designed for study purposes with the use of Clinical Trial Processor software

TABLE 1
Maternal characteristics at enrollment by number of fetuses and pregnancy characteristics (n = 171; NICHD Fetal Growth Studies: Twins) *(continued)*

Maternal characteristic	Measure
Health insurance, n (%):	
Private/managed care	117 (68.4)
Medicaid, other	40 (23.4)
Self-pay	3 (1.8)
Current student, n (%)	
Yes	14 (8.2)
No	157 (91.8)
Current paid jobs, n (%)	
0	37 (21.6)
1	126 (73.7)
≥2	8 (4.7)
Smoked cigarettes in the past 6 mo, n (%)	
Yes	26 (15.2)
No	144 (84.2)
Missing	1 (0.6)
Frequency of alcoholic beverages in the past week, n (%)	
≥5	0
2−4 times	1 (0.6)
Once	3 (1.8)
Not at all	167 (97.7)
Conception by ovulation stimulation drugs or assisted reproductive technology, n (%)	
In vitro fertilization	46 (26.9)
Intrauterine insemination	10 (5.8)
Medications without in vitro fertilization or intrauterine insemination	11 (6.4)
Donor eggs, donor embryos	13 (7.6)
None of the above	91 (53.2)
Medical diseases, n (%)	
Hypothyroid	11 (6.4)
Hyperthyroid	0
Pregestational diabetes mellitus	3 (1.8)
Asthma	15 (8.8)
Chronic hypertension	10 (5.8)
Cardiovascular disease	1 (0.6)
Anemia	17 (9.9)
Kidney disease	0
Autoimmune disease	6 (3.5)
Epilepsy	1 (0.6)

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TABLE 1
Maternal characteristics at enrollment by number of fetuses and pregnancy characteristics (n = 171; NICHD Fetal Growth Studies: Twins) *(continued)*

Maternal characteristic	Measure
HIV	1 (0.6)
Eating disorder	3 (1.8)
Mood disorder, psychiatric disorder, anxiety or depression	17 (9.9)
Other medical condition	27 (15.8)
Pregnancy outcome(twin/twin), n (%)	
Live birth at ≥20 wk/live birth at ≥20 wk	152 (88.9)
Live birth at ≥20 wk/fetal death at ≥ 20 wk	3 (1.8)
Fetal death at ≥20 wk/fetal death at ≥20 wk	3 (1.8)
Fetal death ≥20 wk/miscarriage <20 wk	1 (0.6)
Fetal death, unknown gestational age/fetal death, unknown gestational age	1 (0.6)
Miscarriage at <20 wk/miscarriage at <20 wk	1 (0.6)
Miscarriage/unknown outcome	1 (0.6)
Voluntary termination or fetal reduction/same	1 (0.6)
Voluntary termination or fetal reduction/unknown outcome	3 (1.8)
Unknown outcome/unknown outcome	5 (2.9)
Neonatal sex, n (%)	
Singleton male or twins male/male	45 (26.3)
Singleton female or twins female/female	41 (24.0)
Twins male/female	70 (40.9)
Twins male/unknown[b]	1 (0.6)
Twins unknown[c]	14 (8.2)
Zygosity (same-sex twins only), n (%)	
Monozygotic	15 (8.8)
Dizygotic[d]	133 (77.8)
Missing with same sex twins[e]	8 (4.7)
Missing neonatal sex and zygosity	15 (8.8)

[a] Data are given as mean ± standard deviation; [b] Twin A was an antepartum fetal death, and twin B was a miscarriage at <20 weeks of gestation; [c] Included 11 women who deactivated from the study; 2 women with live birth of both twins, but neonatal sex not recorded, and 1 pregnancy with no chart review performed; so neonatal outcome and sex unknown; [d] Includes 70 male and female twin pairs and 63 same sex pairs that resulted as dizygotic by zygosity testing; [e] Zygosity testing not performed because of miscarriage/death (n = 4), participant refusal (n = 3), or failed DNA extraction because of inadequate sample (n = 1).

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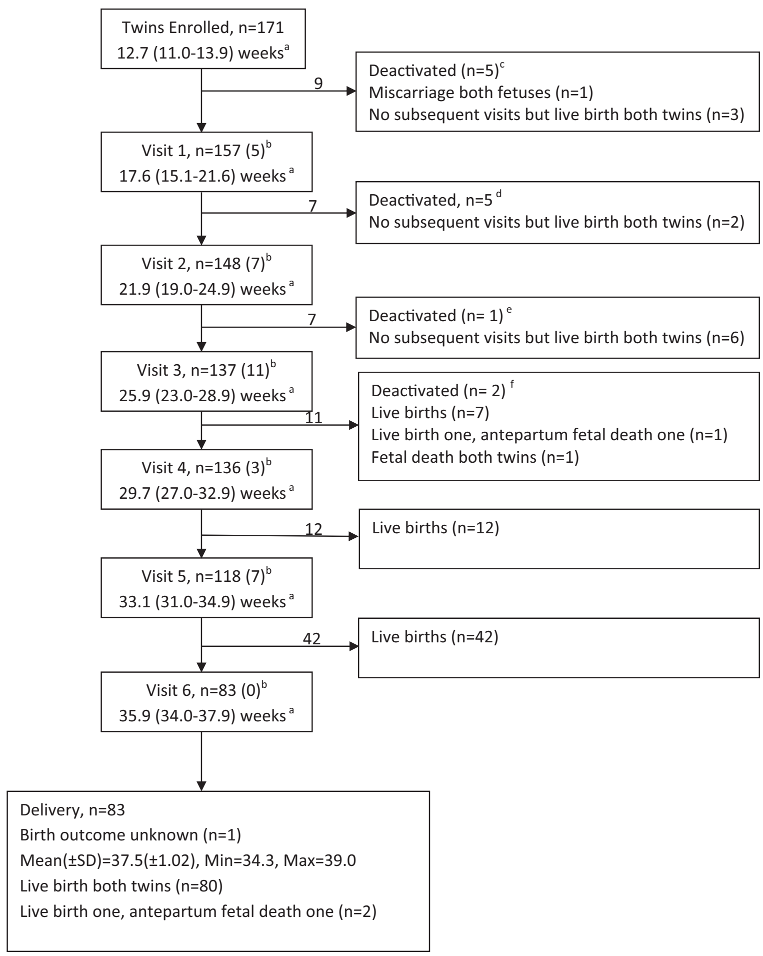
from the Radiological Society of North America. Measurements subsequently were entered manually into a web-based data collection system.

After written informed consent was obtained, women underwent an enrollment visit. The initial study ultrasound imaging was scheduled between 11 weeks 0 days and 13 weeks 6 days of gestation. First-trimester parameters included crown-rump length, biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), humerus length (HL), femur length (FL), placental location, determination of chorionicity, and twin designation. *Study Twin 1* was defined and labelled as the fetus closest to the cervical os. In-person interviews were conducted to obtain information on sociodemographic characteristics; medical, reproductive, and pregnancy histories, and health and lifestyle behaviors. Women were then assigned randomly to receive sonograms according to 1 of the following 2 schedules: schedule A: 16, 20, 24, 28, 32, and 35 weeks or schedule B: 18, 22, 26, 30, 34, and 36 weeks. Women were expected to have a sonogram scheduled within ±1 week of the targeted gestational age. Women were assigned randomly to 1 of 2 schedules to ensure adequate representation of gestational weeks for statistical modeling. Care was undertaken to allow the research ultrasound images to report to the clinical side if needed, recognizing the high-risk status of twin pregnancies. Follow-up sonograms included core biometric measurements (BPD, HC, AC, FL). The HC/AC ratio was calculated for examination of trends in growth patterns over time. Estimated fetal weight (EFW) was calculated with the Hadlock formula, which incorporates HC, AC, and FL.[11]

Several steps were performed to maintain consistency of study twin designation. At each follow-up visit, a series of identifying information was collated at the end of the examination that included fetal sex, identification of anatomic differences, placental location and cord insertion, fetal position, size, location, and presentation/lie. The list was autopopulated for fetus A or B. The sonographer then assigned each twin to the corresponding Study Twin Identification number (1 or 2) based on information from the previous sonogram. At delivery, care was taken to match same-sex twins with their designation in the longitudinal component of the study with the use of an established protocol: a designation form was completed that collected information on birth date and time, neonatal sex, birthweight, presentation at birth (vertex, breech, or unable to determine), whether an external or internal version was performed before delivery, and identifying anatomic differences. Placental samples, or buccal swabs if the placenta was not available,

FIGURE 1
Flow diagram (NICHD Fetal Growth Studies: Twins)



All data were included in the analysis up until the time that each of the women had an event (eg, delivery, deactivation). [a] Gestational age (range) in weeks in which the visits occurred; [b] The numbers in the parentheses indicate women who missed the visit; [c] Reasons for deactivation: voluntary termination of both fetuses (n = 1), voluntary termination of 1 fetus (n = 1), miscarriage of 1 fetus (n = 1), moved (n = 1), and refusal to continue (n = 1); [d] Reasons for deactivation: voluntary termination of 1 fetus (n = 2), miscarriage/stillbirth (intrapartum fetal death) of both twins (n = 2), antepartum fetal death of both twins (n = 1); [e] Reasons for deactivation: moved (n = 1); [f] Reasons for deactivation: antepartum fetal death (n = 1), refusal to continue (n = 1).

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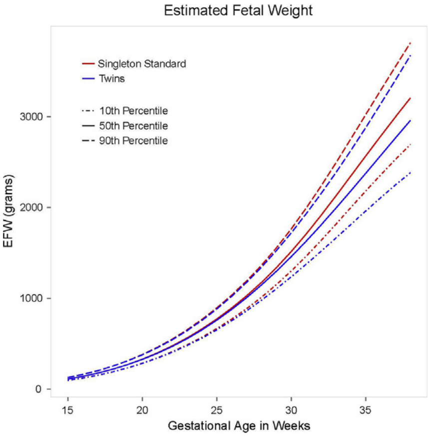
were obtained for zygosity determination with the use of standard single tandem repeat identifier kits (Applied Biosystems AmpFLSTR Identifiler PCR Amplification Kit; ThermoFisher Scientific, Waltham, MA), for all same-sex twin pairs.

A 10% random sample of ultrasound images was selected for quality control review of core biometrics (CRL, BPD, HC, AC, FL) with the use of a similar approach as the NICHD Fetal Growth Studies: Singletons.[12] The correlation between the expert reviewer and site sonographer was ≥88% for all parameters across visits, with 21 of 26 measures having a correlation of ≥95%, which suggests excellent reliability.

In the descriptive analysis, baseline and clinical data were compared for participants by study cohort with the use of chi-square or *t*-tests for categoric or continuous data, respectively. All serial ultrasound data were used to estimate fetal individual parameters, the HC/AC ratio, and EFW by gestational age. Ultrasonography measurements (BPD, HC, AC, HL, FL), the HC/AC ratio, and EFW were log-transformed to stabilize variances across gestational ages and to improve normal approximations for the error structures.

The primary analysis compared fetal growth trajectories for dichorionic twins with 1737 singleton gestations that were included in the NICHD Fetal Growth Studies: Singleton standard.[8] Briefly, the singleton standard enrolled low-risk women and excluded women with certain pregnancy complications or infants with neonatal conditions such as anomalies, aneuploidy, and death. For the twin cohort, all of the data that women contributed to the study were included until they were censored by deactivation, pregnancy loss, or delivery. For modeling twin trajectories, we used linear mixed models with a cubic spline mean structure and a random effects structure that included linear, quadratic, and cubic random effects for the twin pair and an intercept term for the individual fetus within twin pair.[13] This hierarchic random effect structure incorporates correlation for both twin-pair and fetus-within-twin pair in the modeling. The linear mixed models were also used to test for overall differences (ie, global tests) between the twin and singleton trajectories (for EFW and other measurements) with the use of likelihood ratio tests of interaction terms between spline mean structure terms and twin-singleton indicator variables. For the cubic spline mean structure, 3-knot points (25th, 50th, and 75th percentiles) were chosen at gestational ages that evenly split the distributions. For an overall comparison between twin and singleton fetal trajectories, the singleton standards were weighted to have the same distribution of race/ethnicity as in the twin sample. For those ultrasound measurements for which there were significant global tests for differences between twins and singletons, we tested for week-specific differences using Wald tests that were computed at each gestational age. These

FIGURE 2
Distribution of estimated fetal weight by number of fetuses and gestation (NICHD Fetal Growth Studies: Twins)



Estimated 10th, 50th, and 90th percentiles for fetal weight for dichorionic twin gestations and singleton gestations that were included in the standard, as estimated from linear mixed models with log-transformed outcomes and cubic splines. For an overall comparison between twins and singleton fetal trajectories, the singleton standards were weighted to have the same racial/ethnic distribution as observed in the twin cohort.

EFW, estimated fetal weight.

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tests were conducted on the estimated curves with and without adjustments for maternal characteristics: age in years, race/ethnicity, height (centimeters) and pregravid weight (kilograms), parity, full-time employment/student status (yes/no), marital status (married/living as married vs not), health insurance (private/managed vs Medicaid/other), income (≤$29,999, $30,000–49,999, $50,000–$74,999, $75,000–$99,999, and ≥$100,000), education (<high school, high school, some college, college undergraduate, and postgraduate college), and infant sex (male or female). We used multiple imputation (with 20 imputations) to account for missing covariates when we performed covariate-adjusted tests for week-specific twin vs singleton differences in fetal growth curves.[14]

TABLE 2
Percentiles for dichorionic twin fetal anthropometric measurements by gestational age

	Percentile				
Gestational age, wk	10th	25th	50th	75th	90th
Biparietal diameter (mm)—dichorionic twin					
11	13.6	14.2	14.9	15.6	16.3
12	17.2	17.9	18.8	19.7	20.5
13	20.9	21.7	22.7	23.8	24.7
14	24.5	25.5	26.6	27.8	28.9
15	28.0	29.1	30.4	31.6	32.9
16	31.4	32.6	33.9	35.3	36.6
17	34.6	35.8	37.3	38.8	40.2
18	37.8	39.1	40.6	42.2	43.7
19	40.9	42.3	43.9	45.6	47.1
20	43.9	45.4	47.1	48.8	50.5
21	46.9	48.5	50.2	52.1	53.8
22	49.8	51.4	53.3	55.2	57
23	52.7	54.4	56.3	58.3	60.1
24	55.5	57.3	59.3	61.3	63.3
25	58.3	60.1	62.2	64.4	66.4
26	61.0	62.9	65.1	67.3	69.4
27	63.7	65.6	67.9	70.2	72.4
28	66.2	68.2	70.6	73.0	75.3
29	68.6	70.7	73.1	75.7	78.0
30	70.8	73.0	75.5	78.2	80.6
31	72.8	75.1	77.7	80.4	82.9
32	74.7	77.0	79.7	82.5	85.1
33	76.4	78.8	81.5	84.4	87.1
34	77.9	80.4	83.2	86.1	88.9
35	79.3	81.9	84.8	87.8	90.6
36	80.7	83.3	86.3	89.4	92.3
37	82.0	84.7	87.8	91	93.9
38	83.3	86.1	89.3	92.6	95.7
Head circumference (mm) — dichorionic twin					
11	52.8	55.0	57.5	60.1	62.5
12	65.4	68.0	70.9	74.0	76.8
13	78.3	81.3	84.7	88.2	91.5
14	91.3	94.5	98.3	102.3	105.9
15	103.9	107.5	111.6	115.9	119.9
16	116.1	120.0	124.4	129.0	133.3

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TABLE 2
Percentiles for dichorionic twin fetal anthropometric measurements by gestational age *(continued)*

Gestational age, wk	Percentile 10th	25th	50th	75th	90th
17	128.0	132.1	136.8	141.7	146.2
18	139.9	144.2	149.1	154.2	158.9
19	151.6	156	161.2	166.5	171.4
20	163.1	167.7	173	178.5	183.6
21	174.4	179.2	184.7	190.3	195.5
22	185.5	190.4	196.0	201.8	207.2
23	196.3	201.4	207.2	213.2	218.7
24	207.1	212.3	218.2	224.3	230
25	217.7	223.0	229.1	235.4	241.2
26	228.0	233.5	239.8	246.3	252.2
27	238.1	243.8	250.2	256.9	263
28	247.7	253.6	260.3	267.1	273.4
29	256.9	262.9	269.8	276.9	283.4
30	265.4	271.7	278.8	286.1	292.9
31	273.3	279.7	287.1	294.7	301.6
32	280.4	287.1	294.7	302.6	309.8
33	286.9	293.8	301.7	309.8	317.3
34	292.7	299.9	308.1	316.4	324.2
35	298.0	305.4	313.8	322.5	330.5
36	302.8	310.4	319.1	328.1	336.4
37	307.0	315.0	324.0	333.3	341.9
38	310.9	319.1	328.5	338.3	347.2
Abdominal circumference (mm)—dichorionic twin					
11	38.9	41.2	43.9	46.8	49.6
12	48.7	51.5	54.8	58.3	61.6
13	59.1	62.4	66.3	70.4	74.3
14	70.0	73.8	78.2	82.9	87.4
15	81.0	85.2	90.2	95.6	100.6
16	92.0	96.7	102.3	108.1	113.7
17	103.0	108.2	114.2	120.6	126.7
18	114.0	119.6	126.2	133.1	139.6
19	125.0	131.0	138	145.4	152.4
20	135.9	142.3	149.8	157.6	165
21	146.5	153.3	161.2	169.6	177.4
22	157.0	164.1	172.5	181.2	189.5
23	167.2	174.7	183.5	192.7	201.4
24	177.2	185.1	194.3	204.0	213.1

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Because decreased BPD, despite similar HC measurements in twins compared with singletons, has previously been reported,[15] we examined breech position in relation to BPD by including breech position as a time-dependent covariate in the linear mixed model described earlier. This analysis addresses the question of whether the mean BPD measurement changes because of the breech position of the fetus.

Last, we evaluated the degree of reclassification in small for gestational age (SGA), defined as <10th percentile, that would be introduced if fetal growth estimation for twins was based on an unweighted singleton non-Hispanic white standard similar to our previous study.[8]

To assess the robustness of the findings in a low-risk cohort of twins, we performed a sensitivity analysis that was limited to fetuses from women without any preexisting or obstetric diseases (eg, gestational diabetes mellitus, hypertensive disorders) who were not smoking or drinking during pregnancy and who delivered ≥37 weeks of gestation. We also repeated the EFW comparison with the singleton standard that was limited to dizygotic twin pregnancies, which was defined at birth as unlike-sex or same-sex pairs with dizygosity confirmed by placental pathologic testing. Finally, we compared EFW trajectories for twin pregnancies that were conceived spontaneously, by IVF (excluding donor eggs or embryos), or by other medically assisted reproductive techniques.

A post hoc power analysis demonstrated that we had extremely high power to detect differences. Specifically, with the use of an approximate mean singleton birthweight at 35 weeks of gestation (the average age of delivery of twins) of 2800 g, standard deviation of 440 g,[16] and an assumed conservative 10% increase in standard deviation for twins, we had 95% power for detecting a 5% difference in weight (as a proxy of trajectories) between the cohort of 1731 singletons in the standard cohort and our cohort of 171 pairs of dichorionic twins and a 2-tail probability value at <.05. Further, the aforementioned calculations are extremely conservative because they use a single estimate at birth rather than longitudinal trajectories.

All analyses were implemented with the use of SAS software (version 9.4; SAS Institute, Inc, Cary, NC) or R (version 3.1.2; available at http://www.R-project.org). Significance was defined by a 2-tail probability value of <.05.

Results

There were 171 women with dichorionic twins who were recruited into the study, of whom 152 (88.9%) delivered 2 live born infants (Table 1; Figure 1). The flow diagram for study participants is presented in Figure 1. Women underwent a median of 5 ultrasound scans. The women with dichorionic twins were primarily non-Hispanic white (54.5%), followed by non-Hispanic black (21.1%), Hispanic (19.3%), and Asian (4.7%) with an average age of 31.6 ± 6.1 years and prepregnancy body mass index of 28.6 ± 7.0 kg/m^2 (Table 1). Most women in the cohort had a college or postgraduate education, a family income of ≥$75,000, and private or managed healthcare insurance and were employed. Conception was spontaneous in 53.2% of the dichorionic twin pregnancies; 26.9% were conceived by IVF without donor eggs or embryos, 7.6% by IVF with donor eggs or embryos, 5.8% by intrauterine insemination, and 6.4% by ovulation induction without IVF or intrauterine insemination. With regard to complications, 5.8% of women had chronic hypertension; 1.8% women had pregestational diabetes mellitus, and 38.0 % women had a prepregnancy body mass index of ≥30 kg/m^2. The mean ± SD age at delivery was 35.1 ± 4.3 weeks of gestation. There were 15 monozygotic twins (8.8%), 133 dizygotic twins (77.8%), and 23 twins with unknown zygosity (13.5%); the reasons are listed in Table 1. Placental pathologic information was available for 137 twin pairs (80.1%) and resulted as 134 (97.8%) dichorionic and 3 (2.2%) monochorionic twins.

Figure 2 presents the curves for EFW that include the 10th, 50th, and 90th percentiles for dichorionic twins and

TABLE 2
Percentiles for dichorionic twin fetal anthropometric measurements by gestational age *(continued)*

Gestational age, wk	Percentile 10th	25th	50th	75th	90th
25	187.2	195.4	205.1	215.2	224.7
26	197.0	205.6	215.7	226.2	236.2
27	206.6	215.6	226.1	237.1	247.5
28	216.0	225.4	236.4	247.9	258.7
29	225.2	235.0	246.5	258.4	269.7
30	234.3	244.5	256.4	268.8	280.6
31	243.1	253.8	266.1	279.1	291.3
32	251.8	262.9	275.7	289.2	301.9
33	260.4	271.8	285.2	299.2	312.3
34	268.7	280.6	294.4	309.0	322.6
35	276.9	289.2	303.6	318.6	332.8
36	284.9	297.7	312.5	328.2	342.9
37	292.7	306.0	321.4	337.6	352.9
38	300.2	314.0	330.1	347.0	363.0
Femur length (mm) — dichorionic twin					
11	3.5	3.8	4.1	4.4	4.8
12	5.6	6.0	6.5	7.0	7.5
13	8.3	8.8	9.5	10.2	10.9
14	11.2	11.9	12.8	13.7	14.5
15	14.3	15.2	16.1	17.2	18.2
16	17.4	18.3	19.4	20.6	21.7
17	20.3	21.4	22.6	23.9	25.1
18	23.3	24.4	25.7	27.1	28.4
19	26.2	27.4	28.8	30.3	31.6
20	29.0	30.3	31.8	33.3	34.8
21	31.7	33.0	34.6	36.2	37.8
22	34.2	35.6	37.3	39.0	40.6
23	36.6	38.1	39.8	41.7	43.4
24	38.9	40.5	42.3	44.3	46.1
25	41.1	42.8	44.7	46.8	48.7
26	43.2	45.0	47.1	49.3	51.3
27	45.3	47.2	49.4	51.7	53.9
28	47.3	49.3	51.6	54	56.3
29	49.2	51.3	53.7	56.3	58.7
30	51.1	53.3	55.8	58.5	61.0
31	52.9	55.2	57.8	60.6	63.2
32	54.7	57.1	59.8	62.6	65.3

Grantz et al. Dichorionic twin growth. Am J Obstet Gynecol 2016. *(continued)*

TABLE 2
Percentiles for dichorionic twin fetal anthropometric measurements by gestational age *(continued)*

	Percentile				
Gestational age, wk	10th	25th	50th	75th	90th
33	56.5	58.9	61.6	64.6	67.3
34	58.2	60.6	63.5	66.4	69.3
35	59.8	62.3	65.2	68.3	71.1
36	61.3	63.9	66.9	70.0	73.0
37	62.8	65.4	68.5	71.8	74.8
38	64.0	66.8	70.1	73.5	76.7
Humerus length (mm) — dichorionic twin					
11	3.5	3.8	4.1	4.5	4.8
12	5.9	6.3	6.8	7.3	7.8
13	8.7	9.3	10.0	10.7	11.4
14	11.8	12.5	13.4	14.4	15.3
15	14.9	15.8	16.8	17.9	18.9
16	17.8	18.8	19.9	21.1	22.3
17	20.5	21.6	22.8	24.1	25.4
18	23.2	24.3	25.6	27.0	28.3
19	25.8	26.9	28.3	29.7	31.1
20	28.2	29.4	30.9	32.4	33.7
21	30.5	31.8	33.3	34.8	36.3
22	32.7	34.0	35.5	37.1	38.6
23	34.7	36.1	37.7	39.3	40.8
24	36.7	38.1	39.7	41.4	43.0
25	38.5	40.0	41.7	43.5	45.1
26	40.2	41.8	43.6	45.4	47.2
27	41.9	43.5	45.4	47.4	49.2
28	43.5	45.2	47.1	49.2	51.1
29	44.9	46.7	48.8	51.0	53.0
30	46.4	48.2	50.4	52.7	54.8
31	47.7	49.7	52.0	54.3	56.6
32	49.1	51.1	53.5	55.9	58.2
33	50.3	52.4	54.9	57.4	59.9
34	51.5	53.7	56.2	58.9	61.4
35	52.7	54.9	57.6	60.3	62.8
36	53.8	56.1	58.8	61.6	64.2
37	54.8	57.2	60.0	62.9	65.6
38	55.8	58.2	61.1	64.1	66.9

Grantz et al. Dichorionic twin growth. Am J Obstet Gynecol 2016. *(continued)*

singletons who were included in the NICHD Fetal Growth Studies: singleton standard. All percentiles for dichorionic twin fetal measurements by gestational age are provided in Table 2, along with significance testing for pairwise comparisons in Table 3. Significant differences were observed between the EFW curves for dichorionic twins and singletons (Figure 2; global $P < .001$). The mean EFW for twins deviated from that of the singletons beginning at 32 weeks of gestation and continued to diverge through 38 weeks of gestation (Table 3). At 32 weeks of gestation, the EFW for the 10th, 50th, and 90th percentiles were 1518, 1807, and 2151 g for dichorionic twins and 1636, 1912, and 2235 g for singletons in the weighted standard, respectively. At 35 weeks of gestation, which is the average age at delivery for twins, the mean EFW for twins was 191 g smaller than singletons ($P < .001$), and the 10th percentile was 220 g smaller than singletons (10th, 50th, and 90th percentiles were 1960, 2376, and 2879 g, respectively, for dichorionic twins and 2180, 2567, and 3022 g, respectively, for singletons in the race/ethnicity weighted standard).

The curves for the individual fetal measurements were statistically significantly different between dichorionic twins and singletons (Figure 3; global $P < .001$ for all). The BPD was smaller in twins compared with singletons at 11 weeks of gestation, although larger than singletons at 16–25 weeks of gestation; most differences were ≤1 mm. The BPD was also smaller than in singletons beginning at 34–36 weeks of gestation, with differences of ≤2 mm. Breech twin fetuses had slightly larger BPD measurements than nonbreech twins, regardless of whether the fetuses were assessed at 11–27 weeks of gestation ($P = .002$) or 28–38 weeks of gestation ($P = .004$). The AC was smaller in twins compared with singletons at 11 weeks of gestation, with a difference of 1.4 mm. The AC also became statistically progressively smaller in twins beginning at 32 weeks of gestation, and this effect continued through 37 weeks of gestation, reaching a mean difference of 12.1 mm at 37 weeks of gestation.

Comparisons at each gestational age did not identify any statistically significant differences in HC or FL for twins compared with singletons. The HL in twins was also slightly shorter at 11 weeks of gestation and slightly longer from 13–14 weeks of gestation, with differences of ≤0.3 mm. The mean HC/AC ratio declined for both twins and singletons over gestation but was larger for twins beginning at 33 and continuing through 38 weeks of gestation, which suggests a more asymmetric pattern of growth compared with singletons. At 35 weeks of gestation, the mean HC/AC ratio in twins compared with singletons was 1.033 vs 1.005, respectively ($P = .004$). Male fetuses had an EFW that was higher than female fetuses; however, this differential was similar for twins and singletons.

We evaluated the percentage of dichorionic twins who would be classified at <10th percentile with the study-generated singleton non-Hispanic white standard (Figure 4). Beginning at 19 weeks of gestation, the percentage of dichorionic twins with an EFW classified at <10th percentile exceeded 10%. For example, at 32 weeks of gestation, at the time when the mean EFW for the twin average became smaller than the singletons, 34% of twins would be classified as <10th percentile. At 35 weeks of gestation, 38% of dichorionic twins would be classified as <10th percentile.

In a sensitivity analysis that was limited to 36 low-risk women with uncomplicated dichorionic twin pregnancies that delivered at ≥37 weeks of gestation, the pattern of increasing disparity in the mean EFW of twins compared with singletons persisted, beginning at 32 weeks of gestation and continuing through term ($P = .002$). When we compared the EFW trajectories for 133 certain dizyogotic twins with the singleton standard, the results were similar to the main analysis ($P < .001$). Also, no statistically significant differences were observed in twin EFW growth trajectories based on method of conception (spontaneous, IVF, or other assisted reproductive techniques).

TABLE 2
Percentiles for dichorionic twin fetal anthropometric measurements by gestational age *(continued)*

	Percentile				
Gestational age, wk	10th	25th	50th	75th	90th
Estimated fetal weight (g)— dichorionic twin					
15	97.0	103.7	111.7	120.3	128.6
16	122.6	131.1	141.2	152.1	162.6
17	153.7	164.4	177.1	190.7	204.0
18	190.6	203.9	219.7	236.7	253.2
19	233.8	250.2	269.7	290.7	311.0
20	283.9	303.8	327.6	353.2	378.0
21	341.2	365.4	394.1	425.2	455.2
22	406.4	435.4	469.9	507.3	543.4
23	479.8	514.3	555.6	600.1	643.3
24	561.9	602.8	651.7	704.5	755.8
25	653.0	701.1	758.7	821.1	881.6
26	753.0	809.3	876.9	950.1	1021.2
27	861.8	927.5	1006.2	1091.7	1174.8
28	979.1	1055.1	1146.6	1245.9	1342.7
29	1104.2	1191.9	1297.5	1412.4	1524.6
30	1236.4	1337.0	1458.4	1590.8	1720.2
31	1374.7	1489.6	1628.5	1780.4	1929.2
32	1517.8	1648.4	1806.7	1980.2	2150.6
33	1664.2	1812.0	1991.6	2189.1	2383.5
34	1812.3	1978.8	2181.8	2405.7	2626.7
35	1960.3	2147.1	2375.5	2628.3	2878.6
36	2106.4	2314.9	2570.9	2855.1	3137.8
37	2248.1	2480	2765.9	3084.7	3402.9
38	2382.5	2639.8	2958.4	3315.5	3673.5
Head circumference/ abdominal circumference— dichorionic twin					
11	1.187	1.242	1.306	1.373	1.437
12	1.18	1.233	1.294	1.359	1.419
13	1.167	1.218	1.277	1.34	1.398
14	1.152	1.201	1.258	1.318	1.374
15	1.135	1.182	1.237	1.295	1.349
16	1.118	1.163	1.217	1.272	1.324
17	1.102	1.146	1.197	1.251	1.301
18	1.088	1.131	1.181	1.233	1.282
19	1.076	1.118	1.167	1.217	1.265

Grantz et al. Dichorionic twin growth. Am J Obstet Gynecol 2016. *(continued)*

TABLE 2
Percentiles for dichorionic twin fetal anthropometric measurements by gestational age *(continued)*

Gestational age, wk	Percentile 10th	25th	50th	75th	90th
20	1.065	1.107	1.155	1.204	1.251
21	1.057	1.097	1.144	1.193	1.239
22	1.049	1.089	1.136	1.184	1.23
23	1.042	1.082	1.128	1.177	1.222
24	1.036	1.076	1.122	1.17	1.215
25	1.031	1.071	1.116	1.164	1.209
26	1.026	1.066	1.111	1.159	1.203
27	1.021	1.06	1.106	1.153	1.198
28	1.015	1.055	1.100	1.148	1.192
29	1.009	1.048	1.094	1.141	1.186
30	1.002	1.041	1.086	1.134	1.178
31	0.993	1.033	1.078	1.125	1.169
32	0.984	1.023	1.068	1.115	1.159
33	0.973	1.012	1.057	1.103	1.147
34	0.962	1.001	1.045	1.092	1.135
35	0.951	0.989	1.033	1.079	1.122
36	0.939	0.977	1.021	1.067	1.11
37	0.928	0.966	1.009	1.055	1.098
38	0.916	0.954	0.998	1.044	1.087
Femoral length/abdominal circumference — dichorionic twin					
11	0.079	0.086	0.093	0.102	0.11
12	0.102	0.11	0.119	0.129	0.139
13	0.124	0.133	0.143	0.154	0.165
14	0.142	0.152	0.163	0.175	0.187
15	0.157	0.167	0.179	0.191	0.203
16	0.168	0.178	0.190	0.202	0.214
17	0.176	0.186	0.197	0.210	0.222
18	0.182	0.192	0.204	0.216	0.228
19	0.187	0.197	0.208	0.221	0.232
20	0.190	0.200	0.212	0.224	0.236
21	0.193	0.203	0.214	0.226	0.238
22	0.195	0.204	0.216	0.228	0.239
23	0.196	0.205	0.217	0.229	0.240
24	0.196	0.206	0.217	0.229	0.241
25	0.196	0.206	0.218	0.23	0.241
26	0.196	0.206	0.218	0.23	0.242

Grantz et al. Dichorionic twin growth. Am J Obstet Gynecol 2016. *(continued)*

Comment

In our prospective cohort study of dichorionic twin gestations, the EFW and AC differed from those of singletons beginning at 32 weeks of gestation through delivery. The BPD was slightly larger in twins earlier in mid pregnancy but was smaller from 34–36 weeks of gestation; the HC remained similar to singletons. The FL was not different in twins. The pattern of growth was more asymmetric in twins, which was characterized by the larger HC/AC ratio compared with singletons at >32 weeks of gestation.

Our finding that the mean EFW deviated from that of singletons at approximately 32 weeks of gestation is similar to studies that have used clinical ultrasound data and were restricted to dichorionic twins. Min et al[17] found that the mean EFW for dichorionic twins became smaller than singletons at approximately 30 weeks of gestation, although the mean EFWs from 30–38 weeks of gestation were lower than in our study, probably because of their inclusion of more minority women. Shivkumar et al[18] studied a Canadian population from a single hospital and found that the mean EFW became smaller for dichorionic twins compared with a published singleton chart from Hadlock et al[19] that started at 32 weeks of gestation, which is similar to our sensitivity analysis of low-risk dichorionic twins. The mean twin EFWs in our study were generally lower than another US prospective study of 35 twins published in 1987.[5] These dissimilar results may be at least partly due to differences in study populations (because ours focused on a more contemporary population), accuracy of measurements that included shorter measurements with newer ultrasound machines because of a narrower beam width,[20] or other potential confounders. In the present study, a standardized ultrasound protocol was implemented to ensure high-quality measurements and was confirmed by our quality-control analysis. Importantly, we directly compare dichorionic twin fetuses to singletons from healthy pregnancies with the use of novel

TABLE 2
Percentiles for dichorionic twin fetal anthropometric measurements by gestational age *(continued)*

Gestational age, wk	Percentile 10th	25th	50th	75th	90th
27	0.196	0.206	0.218	0.23	0.242
28	0.196	0.206	0.218	0.23	0.242
29	0.196	0.206	0.218	0.23	0.242
30	0.195	0.205	0.217	0.23	0.242
31	0.195	0.205	0.217	0.229	0.241
32	0.194	0.204	0.216	0.229	0.241
33	0.194	0.204	0.216	0.228	0.240
34	0.193	0.203	0.215	0.227	0.239
35	0.193	0.203	0.214	0.227	0.238
36	0.192	0.202	0.213	0.226	0.238
37	0.191	0.201	0.213	0.225	0.237
38	0.190	0.200	0.212	0.225	0.236

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methods for the estimation of growth and EFW.

Compared with singletons, dichorionic twins had a smaller AC and EFW beginning at 32 weeks of gestation but similar HC and long bones. These findings are consistent with neonatal anthropometric data in which HC and length of twins were found to be comparable with singletons at birth.[21] Compared with appropriate-for-gestational-age singletons, birthweights for concordant twins have been found to be lower, but the HC and body length to be similar.[22] Our findings are also similar to a prospective ultrasound study at a single US center of 103 concordant twin pairs (albeit chorionicity and maternal race were not reported) that were compared with published singleton references.[23] It has previously been reported that dolichocephalic breech twins have smaller BPDs but similar HC, which is a phenomenon that is attributed to a compression effect from fetal crowding.[15,18] This theory is supported by the observation that dolichocephaly is associated with both breech presentation and oligohydramnios.[24,25] Interestingly, in our study, twin fetuses in the breech presentation had larger BPDs compared with nonbreech twins, which indicates that breech presentation did not explain the differences between the smaller BPD in twins compared with singletons beginning at 32 weeks of gestation.

The HC/AC ratio has been described as a way to distinguish early-onset, symmetric growth restriction that is associated with factors, such as aneuploidy and intrauterine infections, from later onset asymmetric cases that are associated with placental insufficiency.[26,27] Our finding that the HC/AC ratio in twins became larger than singletons starting at 33 weeks of gestation is consistent with a constrained and comparatively asymmetric growth pattern in twins.

The progressively asymmetric pattern of slower growth in dichorionic twins is consistent with the concept that the intrauterine environment is less capable of sustaining adequate growth in twin fetuses as the pregnancy progresses.[28] Maternal constraint is a known phenomenon whereby the genetic potential of fetal growth is not fully achieved, such as that associated with short stature and nulliparity.[29] In 1 study of twin growth that was estimated at 28 weeks of gestation, fetuses with a HC, AC, or FL below the 10th percentile were shorter in childhood at age 3 years; those fetuses with AC or FL below the 10th percentile had evidence for stunting at age 3 years, which was indicated by lower weight for age percentiles and z-scores compared with normally grown twin fetuses.[30] Reassuringly, there were no differences in mental or motor development. Long-term surveillance is needed to determine whether twin neonates who are born smaller than gestational age-matched singletons, but within a normal reference range of birthweight, experience adverse future health sequelae.

The sporadic minimal twin-singleton differences indicate that the differences in the mean between the 2 groups are highly statistically significant; however, these small differences may not be detectable on an individual level or have clinical meaning. We acknowledge that the differences could be due to unmeasured confounding but may support a biologic effect. Blickstein[31] reviewed birthweight data and concluded that, because the combined birthweight of the pair of fetuses in twins exceeds that of the average singleton, the entire twin pregnancy represents more of a growth promotion. Perhaps the maternal body is primed early on to recruit additional resources for multiple fetuses, which may explain the larger measurements of some parameters in twins compared with singletons earlier in gestation.

Our rate of 97.8% confirmation of dichorionic twins when placental pathologic information was available is consistent with what has been reported in the literature: 95.6% at a single site and 77.3–100% in other studies.[32] The few monochorionic twins in the series did not account for the differences that were found between the singletons and twins. The major strengths of our study were its prospective design with longitudinal measurement of fetal size, systematic attention to twin designation, and implementation of a standardized ultrasound protocol to ensure high-quality measurements (as reflected in our quality control analysis). We also used ante hoc credentialing of sonographers and carefully considered relevant covariates in our analyses.

TABLE 3
Statistical significance for dichorionic twin comparisons with the singleton standard of fetal anthropometric measurements by gestational age

Gestational age, wk	Probability value: Biparietal diameter	Head circumference	Abdominal circumference	Femur length	Humerus length	Estimated fetal weight	Head circumference/ abdominal circumference	Femoral length/ abdominal circumference
11	.008	.085	.017	.883	.016	—	.683	.052
12	.284	.609	.101	.162	.726	—	.342	.001
13	.630	.635	.486	.050	.036	—	.289	.002
14	.172	.367	.844	.136	.029	—	.354	.058
15	.064	.313	.964	.555	.178	.469	.427	.460
16	.028	.312	.944	.668	.876	.340	.499	.736
17	.010	.260	.908	.300	.537	.317	.537	.343
18	<.001	.134	.951	.446	.709	.413	.499	.456
19	<.001	.070	.996	.861	.813	.582	.461	.799
20	<.001	.069	.987	.943	.624	.738	.488	.981
21	<.001	.118	.939	.966	.717	.857	.580	.948
22	<.001	.248	.876	.693	.984	.936	.725	.776
23	.004	.474	.819	.409	.620	.979	.895	.574
24	.015	.710	.788	.244	.371	.994	.947	.427
25	.039	.866	.784	.181	.254	1.000	.825	.353
26	.080	.944	.778	.170	.207	.972	.763	.339
27	.152	.971	.736	.187	.198	.891	.784	.384
28	.279	.982	.630	.209	.205	.731	.912	.494
29	.504	.992	.450	.204	.205	.493	.836	.671
30	.862	.931	.252	.166	.190	.252	.519	.911
31	.681	.829	.110	.121	.169	.096	.257	.794
32	.302	.711	.041	.090	.154	.030	.106	.507
33	.113	.625	.015	.076	.143	.009	.040	.305
34	.048	.603	.007	.068	.124	.004	.014	.187
35	.031	.675	.003	.059	.092	.002	.004	.119
36	.043	.872	.003	.067	.075	.002	<.001	.100
37	.133	.840	.008	.165	.132	.004	.003	.184
38	.459	.621	.054	.421	.343	.022	.028	.400

Probability values were obtained with the Wald test from the linear mixed model, with adjustment for maternal age, height, weight, parity, race, job, marital status, insurance, income, education, and infant sex. Note: Estimated fetal weight not calculated at <15 weeks of gestation.

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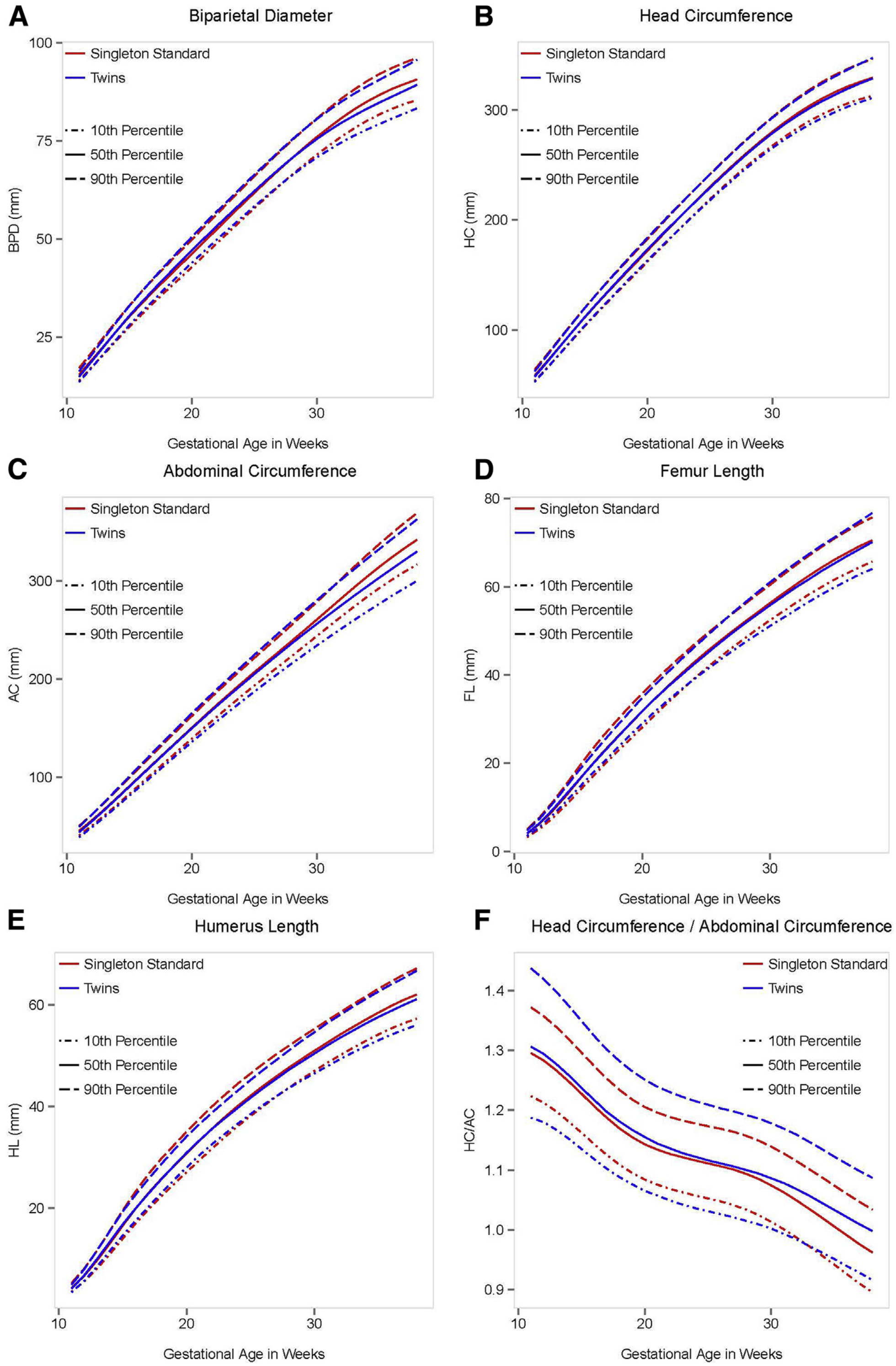
Given the high percentage of twins who are classified as SGA with the use of a singleton non-Hispanic white standard, it could be argued that our findings indicate the need for an ultrasound reference that is specific for twins. However, the clinical challenge is to differentiate SGA that is associated with the normal adaptive process in multiple gestations from fetal growth restriction that is associated with increased morbidity and mortality rates.[28] Future studies with long-term follow up are needed to determine whether dichorionic twin fetuses that are classified as SGA in otherwise uncomplicated pregnancies, with the use of a singleton standard, are at increased risk for short- or long-term morbidity. In the short term, careful consideration should be given before intervening for a small EFW percentile based on a singleton standard in the setting of normal testing, such as umbilical artery Doppler, amniotic

FIGURE 3

Distribution of fetal anthropometric measurements by number of fetuses and gestation (NICHD Fetal Growth Studies: Twins)



Estimated 10th, 50th, and 90th percentiles for the fetal anthropometric parameters for dichorionic twin gestations and singleton gestations that were included in the standard (**a-f**), as estimated from linear mixed models with log-transformed outcomes and cubic splines.

AC, abdominal circumference; *BPD*, biparietal diameter; *FL*, femur length; *HC*, head circumference; *HCAC*, head circumference/abdominal circumference; *HL*, humerus length.

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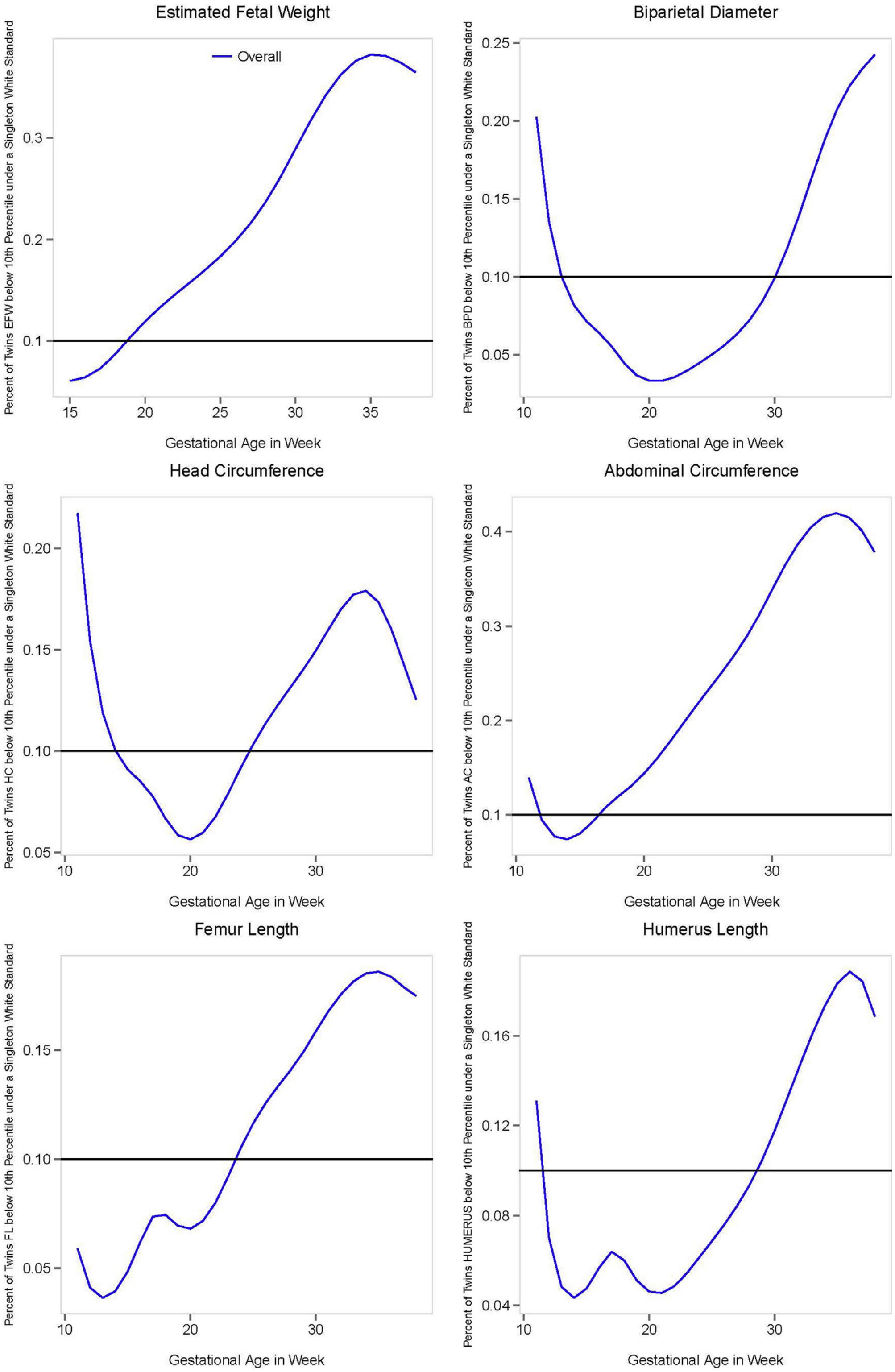
FIGURE 4

Percentage of dichorionic twin fetuses below the 10th percentile of the non-Hispanic white singleton standard



Percentage of twin fetuses below the 10th percentile of the non-Hispanic white singleton standard by gestational age. The difference between the twin-specific curves and the 0.10 line reflect the amount of classification attributed to the use of the non-Hispanic white singleton standard.

AC, abdominal circumference; *BPD*, biparietal diameter; *EFW*, estimated fetal weight; *FL*, femur length; *HC*, head circumference.

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fluid volume, non−stress testing, and biophysical profile. ■

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