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Birth weight references for triplets

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KEY WORDS
Triplets
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Objective: The purpose of this study was to formulate growth references that reflect triplet fetal and neonatal populations at each gestational age by combining serial ultrasonographic estimates of fetal weights and measured birth weights.

Study design: This historical cohort study was based on 188 pregnancies of live-born triplets of ≥23 weeks' gestation. Ultrasonographic fetal weight measures were modeled as a function of gestational age for each infant. Linear regression models were used to fit the data, and weight percentiles were generated.

Results: Well-grown triplets fell substantially below singletons by 30 weeks and twins after 34 weeks. Trichorionic vs monochorionic or dichorionic placentation resulted in 27% higher growth at the 10th %ile, 5% higher growth at the 50th %ile, and 4% higher growth at the 90th %ile by 34 weeks.

Conclusion: The overall pattern of fetal growth for well-grown triplets does not differ from that of singletons and twins until late gestation, confirming that, in utero, well-grown children have similar growth potentials, regardless of plurality.

Multiple births in the United States have been rising dramatically over the past 3decades, reflecting a phenomenon occurring in developed countries around the world. The rate of triplets is rising the fastest, increasing 13% annually between 1990 and 1998, and slowing to 3% annually through 2001.[1] Born an average of 7 weeks earlier, and at half the birth weight of singletons, triplets experience a 12-fold higher risk of dying before their first birthday.[2] Population-based studies indicate that optimal perinatal survival for triplets occurs at earlier gestational ages and lower birth weights than twins or singletons.[3,4] Previous studies of the growth of triplets are limited by either their cross-sectional design,[4,5] or,

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Table I Description of study sample

Study characteristic	Total (n = 188)	Study site: Baltimore (n = 19)	Miami (n = 42)	Ann Arbor (n = 40)	Charleston (n = 45)	Springfield (n = 42)
Maternal age (yr, mean)	31.4 ± 5.3	**31.8 ± 3.8**	**29.1 ± 5.6**	**33.1 ± 5.7**	**33.1 ± 4.5**	**30.6 ± 4.7**
Race						
White, non-Hispanic (%)	76%	**84%**	**38%**	**80%**	**86%**	**95%**
White, Hispanic (%)	10%	**0%**	**45%**	**0%**	**0%**	**0%**
Black (%)	14%	**16%**	**17%**	**20%**	**14%**	**5%**
Parity (mean)	0.7 ± 1.0	0.6 ± 1.0	0.7 ± 0.9	0.8 ± 1.0	0.6 ± 1.0	0.9 ± 1.2
Primiparous (%)	54%	63%	55%	45%	62%	46%
Infertility treatment (%)	72%	**89%**	**60%**	**83%**	**78%**	**57%**
Smokers (%)	4%	5%	2%	0%	4%	10%
Preeclampsia (%)	24%	11%	14%	25%	36%	29%
Height (in, mean)	64.8 ± 3.0	62.0 ± 4.7	65.1 ± 2.5	64.8 ± 2.3	65.5 ± 2.6	65.1 ± 2.8
Pregravid weight (lb, mean)	147.6 ± 38.3	**125.1 ± 21.1**	**148.6 ± 39.7**	**148.1 ± 33.8**	**144.4 ± 35.4**	**160.0 ± 45.8**
Body mass index (mean)	24.7 ± 6.1	23.1 ± 4.1	24.6 ± 6.1	24.8 ± 5.6	23.6 ± 5.5	26.6 ± 7.5
BMI <19.8 (%)	17%	16%	17%	13%	28%	10%
BMI 19.8-25.9 (%)	53%	63%	51%	58%	53%	44%
BMI 26.0-28.9 (%)	13%	11%	17%	16%	7%	12%
BMI ≥29.0 (%)	17%	10%	15%	13%	12%	34%
Membranes						
Unknown (%)	45%	**53%**	**27%**	**50%**	**11%**	**91%**
Trichorionic (%)	30%	**42%**	**15%**	**23%**	**69%**	**5%**
Dichorionic (%)	19%	**5%**	**46%**	**17%**	**16%**	**2%**
Monochorionic (%)	6%	**0%**	**12%**	**10%**	**4%**	**2%**
Gestation (wk, mean)	32.8 ± 3.3	32.2 ± 3.6	32.9 ± 3.7	32.1 ± 3.3	33 ± 2.7	33.6 ± 3.2
<30 weeks (%)	19%	26%	21%	25%	16%	10%
30-31 weeks (%)	12%	16%	10%	15%	7%	17%
32-33 weeks (%)	29%	21%	17%	25%	38%	40%
34-35 weeks (%)	27%	16%	36%	28%	33%	17%
36-37 weeks (%)	9%	21%	12%	7%	4%	7%
38-39 weeks (%)	2%	0%	2%	0%	2%	2%
≥40 weeks (%)	2%	0%	2%	0%	0%	7%
Average triplet group birthweight (gms, mean)	1720 ± 486	1660 ± 595	1713 ± 514	1651 ± 543	1778 ± 447	1757 ± 386

Values in boldface are significantly different across column categories (P value < .05, two-tailed).

if conducted with serial measurements, do not include birth weight, thereby providing an inaccurate longitudinal picture of growth.[6,7] The purpose of this study was to formulate growth references that reflect triplet fetal and neonatal populations at each gestational age by combining serial ultrasonographic estimates of fetal weight and measured birth weights.

Material and methods

The study sample included all triplets delivered at Johns Hopkins University, Baltimore, Maryland, between December, 1989, and May, 2000; at Jackson Memorial Hospital/University of Miami, Miami, Florida, between January, 1989, and August, 2002; at Medical University of South Carolina, Charleston, South Carolina, between April, 1989, and August, 2002; at University of Michigan, Ann Arbor, Michigan, between September, 1992, and January, 2002; and at Southern Illinois University, Springfield, Illinois, between September, 1983, and November, 2000. The study sample was limited to pregnancies meeting the following inclusion criteria: 1) all 3 infants in each set born alive; 2) ≥23 weeks' gestation, as determined by last menstrual period, first-trimester ultrasonography, or best obstetric estimate (a combination of clinical and ultrasonographic estimates); 3) documented sexes and birth weights of all infants in the set; and 4) absence of major congenital anomalies, as documented by normal findings in the newborn medical record. This study was approved by the institutional review boards at each of the respective institutions.

Study variables

The variables in the abstracted data included study site, maternal age, race (black, white non-Hispanic, and white

Table I (*continued*)

Placental membrane			Reproductive treatment		Race and ethnicity		
Trichorionic (n = 56)	Dichorionic (n = 35)	Monochorionic (n = 12)	Non-infertility (n = 53)	Infertility (n = 133)	White, non-Hispanic (n = 142)	White, Hispanic (n = 19)	Black (n = 26)
32.0 ± 4.7	31.0 ± 5.7	33.4 ± 9.2	30.3 ± 7.1	31.7 ± 4.5	31.7 ± 4.9	30.3 ± 4.7	30.6 ± 7.5
82%	**71%**	**50%**	**53%**	**86%**	100%	0%	0%
4%	**23%**	**33%**	**15%**	**7%**	0%	100%	0%
14%	**6%**	**17%**	**32%**	**7%**	0%	0%	100%
0.6 ± 0.9	0.7 ± 0.8	1.2 ± 0.9	**1.4 ± 1.3**	**0.5 ± 0.7**	**0.6 ± 0.8**	**0.7 ± 0.8**	**1.5 ± 1.6**
56%	51%	25%	**31%**	**62%**	**58%**	**53%**	**31%**
88%	**74%**	**17%**	0%	100%	**80%**	**56%**	**35%**
4%	0%	8%	**11%**	**2%**	4%	5%	4%
21%	20%	42%	26%	24%	26%	11%	23%
65.2 ± 2.6	64.9 ± 2.7	64.8 ± 2.4	65.2 ± 2.7	64.7 ± 3.1	64.6 ± 3.0	64.9 ± 2.8	65.8 ± 2.9
147.0 ± 38.9	143.4 ± 23.1	153.3 ± 35.3	151.5 ± 40.9	146.4 ± 37.6	**145.4 ± 37.6**	**141.4 ± 33.8**	**166.0 ± 42.7**
24.3 ± 6.3	23.9 ± 3.8	25.6 ± 5.0	25.0 ± 5.7	24.6 ± 6.3	24.5 ± 6.1	23.5 ± 5.4	26.9 ± 6.5
20%	17%	17%	16%	18%	19%	16%	4%
56%	57%	25%	44%	56%	52%	63%	46%
11%	17%	33%	20%	9%	12%	11%	21%
13%	9%	25%	20%	17%	17%	10%	29%
0%	0%	0%	**51%**	**42%**	**46%**	**22%**	**54%**
100%	0%	0%	**13%**	**37%**	**32%**	**11%**	**31%**
0%	100%	0%	**17%**	**19%**	**18%**	**45%**	**8%**
0%	0%	100%	**19%**	**2%**	**4%**	**22%**	**8%**
33.3 ± 2.9	31.7 ± 3.6	32.8 ± 3.9	32.7 ± 3.6	32.9 ± 3.1	32.8 ± 3.4	33.8 ± 2.4	32.3 ± 2.9
13%	34%	17%	19%	18%	20%	5%	19%
11%	9%	8%	15%	11%	11%	5%	23%
34%	28%	25%	32%	29%	30%	37%	23%
27%	17%	25%	15%	32%	28%	32%	19%
12%	9%	25%	13%	8%	7%	16%	16%
3%	0%	0%	2%	1%	1%	5%	0%
0%	3%	0%	4%	1%	3%	0%	0%
1809 ± 493	1569 ± 511	1647 ± 467	1659 ± 491	1750 ± 480	1720 ± 496	1885 ± 353	1604 ± 504

Hispanic), smoking during pregnancy, parity (primiparous vs multiparous), infertility treatment, preeclampsia, maternal size variables (height, pregravid weight, and pregravid body mass index (weight/[height]^2), gestational diabetes, chorionicity (unknown, trichorionic, dichorionic, or monochorionic), estimated fetal weights (up to 9), birth weights, weeks' gestation, and infant genders. In accordance with the current methods of the National Center for Health Statistics, the triplets in our study were assigned the race and ethnicity of the mother. The fetal growth of each triplet was estimated from regression curves fit to ultrasonographic fetal weight measurements.

Statistical analysis

Descriptive statistics were calculated to characterize the study sample as a whole, and by study site, chorionicity, infertility treatments, and race and ethnicity. Differences between groups for continuous variables were compared with the Student *t* test (for 2 groups) and analysis of variance (for more than 2 groups); differences for categorical variables were compared with chi-square tests. For cases with unequal variances in the 2-group tests for continuous variables, Behrens-Fisher tests were used instead. All tests were 2-sided, with a significant level of $P = .05$.

Intrauterine growth, based on the ultrasonographic fetal weight measures taken at irregular intervals, was modeled for each infant as a function of gestational age to estimate fetal growth at regular intervals (2-week intervals from 20 to 34 weeks). Linear regression models with quadratic terms and no intercept (to constrain the size to be zero at conception) fit the growth pattern well. However, the ultrasonographic estimates of fetal weights near birth suggested a bias (usually upward and differing by study site) in comparison with actual birth weights. The bias (assumed proportional over the gestational period)

Table II Weight percentiles of triplets by chorionicity and gender

Week	No.	Born (%)	Fetal weight (g) Mean	SD	Percentile 5th	10th	25th	50th	75th	90th	95th
All											
20	345	0	319	105	129	184	267	324	380	446	487
22	345	0	474	118	266	319	408	474	549	622	663
24	345	2	652	140	419	472	565	656	747	825	884
26	337	6	853	169	584	657	747	857	971	1053	1148
28	324	13	1080	203	766	848	947	1084	1213	1317	1405
30	301	25	1330	242	929	1060	1186	1335	1484	1619	1726
32	259	57	1619	292	1125	1287	1440	1626	1810	1959	2091
34	148	88	1876	344	1278	1529	1710	1893	2091	2262	2368
Mono-and dichorionic											
20	72	0	316	107	129	173	258	329	380	429	484
22	72	0	470	122	257	281	406	479	547	591	645
24	72	7	647	143	402	425	568	662	726	812	862
26	67	7	855	174	548	607	761	880	965	1060	1095
28	67	13	1079	209	705	811	950	1097	1192	1317	1395
30	63	21	1335	252	880	1051	1197	1336	1474	1622	1674
32	57	58	1597	313	1024	1271	1405	1601	1760	1959	2088
34	30	83	1822	384	1067	1249	1641	1869	2082	2217	2330
Trichorionic											
20	143	0	330	91	186	237	282	326	396	446	466
22	143	0	486	109	308	361	417	480	554	619	662
24	143	0	664	134	455	504	574	670	752	822	894
26	143	6	865	165	624	668	751	867	978	1051	1120
28	134	12	1099	201	766	848	969	1105	1225	1350	1441
30	126	20	1354	238	929	1054	1205	1372	1499	1646	1752
32	114	58	1657	271	1180	1325	1475	1667	1847	1978	2149
34	60	87	1954	298	1396	1592	1784	1964	2190	2299	2472
Female											
20	174	0	302	100	122	170	257	307	357	422	487
22	174	0	455	112	257	308	398	464	518	578	642
24	174	0	631	133	406	465	550	630	716	777	862
26	174	5	828	162	584	631	719	820	935	1014	1120
28	166	10	1051	195	768	841	921	1035	1181	1279	1369
30	156	23	1299	231	932	1051	1144	1272	1451	1570	1669
32	134	57	1590	277	1151	1271	1429	1588	1748	1902	2044
34	74	89	1851	304	1339	1529	1691	1845	2037	2223	2279
Male											
20	171	0	336	107	136	200	277	345	402	464	489
22	171	0	494	122	281	341	421	497	578	645	674
24	171	5	674	143	447	488	586	679	769	842	902
26	163	8	880	173	597	679	780	894	993	1086	1156
28	158	15	1109	208	705	889	984	1120	1251	1370	1441
30	145	27	1363	249	902	1100	1227	1376	1538	1661	1742
32	125	57	1649	305	1119	1325	1490	1666	1865	1992	2091
34	74	88	1901	379	1067	1536	1755	1939	2172	2330	2390

was estimated for each triplet as the ratio of predicted fetal weight at birth (on the basis of ultrasonographic measurements) to actual birth weight. The ultrasonographic measurements were then corrected for this bias (by dividing by the estimated bias), forcing the regression curve through the actual birth weight. The average estimated bias was 6.5% (± 19.9%) for Baltimore, 2.4% (± 13.8%) for Miami, 11.6% (± 18.6%) for Ann Arbor, 5.0% (± 11.9%) for Charleston, and 22.7% (± 40.1%) for Springfield. For each pregnancy, at least 2 documented ultrasonographic estimates of fetal weights, including 1 before 28 weeks' gestation (to provide more validity for the prediction of early fetal growth), and birth weight were required to fit the regression. About 64% of the infants had at least 2 ultrasonographic measurements of fetal weight, and most (97%) of those had the first one

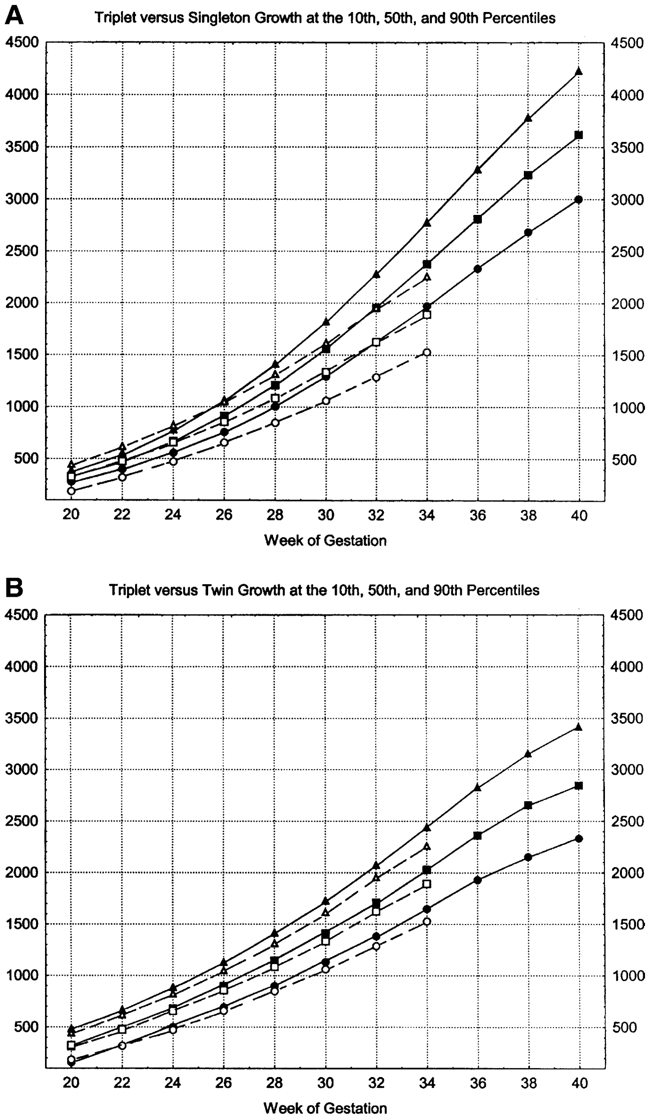

Figure Triangles indicate growth at the 90th percentile, squares at the 50th percentile, and circles at the 10th percentile. **(A)** Singleton growth and **(B)** twin growth is indicated by closed symbols and solid lines. Open symbols and dashed lines indicate triplet growth in both **A** and **B**.

taken before 28 weeks' gestation. Growth beyond 34 weeks was not modeled because of the unreliably small number of cases.

To develop growth references that reflected the triplet fetal and neonatal populations at each gestational age by 2-week intervals from 20 to 34 weeks, weight percentiles were generated for the total study sample, and by chorionicity (monochorionic or dichorionic vs trichorionic), using the estimated fetal growth at regular intervals. The 10th, 50th, and 90th weight percentiles were calculated for our triplet sample and compared with published references for twins[9] and singletons.[10] A comparison of fetal growth and birth weights at the 10th, 50th, and 90th percentiles is shown in Figure 1A for triplets vs singletons, and in Figure 1B for triplets vs twins.

Results

Data were collected from 188 pregnancies of triplets born alive at ≥23 weeks' gestation. A description of the sample by chorionicity, by infertility treatment, and by race and ethnicity is given in Table I. The study sample averaged 1720 ± 486 g birth weight at 32.8 ± 3.3 weeks' gestation; 32% of infants were <1500 g, and 93% were <2500 g; 19% delivered <30 weeks, and 31% <32 weeks; 48% were male; and 5% of mothers developed gestational diabetes. In addition, the 5 study sites differed significantly in mean maternal age, racial and ethnic distribution, percent of women treated for infertility, mean pregravid weight, and placental chorion diagnosis. Among pregnancies with confirmed placental chorion diagnosis, significant differences were noted in racial and ethnic distribution, and percent of women treated for infertility. By infertility treatment, triplet pregnancies differed significantly in racial and ethnic distribution, parity and percent primiparous, percent of smokers, and placental chorion diagnosis. By racial and ethnic group, triplet pregnancies differed significantly by parity and percent primiparous, percent of women treated for infertility, mean pregravid weight, and placental chorion diagnosis.

Triplet growth by placental chorion diagnosis did not differ until late in gestation (Table II). By 34 weeks, growth in pregnancies with monochorionic or dichorionic vs trichorionic placentation was 27% lower (−343 g) at the 10th percentile, 5% lower (−95 g) at the 50th percentile, and 4% lower (−82 g) at the 90th percentile. Males were consistently heavier than females at all gestations.

Compared with our published birth weight reference for twins,[9] based on the same methodology, triplet growth did not deviate substantially at the 10th percentile, 50th percentile, or 90th percentile until 36 weeks. At 34 weeks, triplets fell below twins by 8% (−121 g) at the 10th percentile, by 7% (−137 g) at the 50th percentile, and by 8% (−182 g) at the 90th percentile. Triplets fell substantially below singletons by 26 weeks (15% or −101 g) at the 10th percentile, by 28 weeks (12% or −126 g) at the 50th percentile, and by 30 weeks (13% or −205 g) at the 90th percentile (see Table II).

Comment

Most birth weight references have methodologic limitations, including errors in reported gestational age, biologically implausible birth weight for gestation, inadequate sample size at low gestations, and inadequate statistical modeling techniques. Even the most recent population-based birth weight references, with gestation predominately based on early ultrasound estimates, still only provide a cross-sectional description of birth weights and are not true growth references.[11] Other investigators have acknowledged these problems, and have attempted to construct singleton fetal growth and birth weight references using a combination of prenatal and postnatal measures.[12-14] Because triplets are at much higher risk for fetal growth restriction, which in turn affects their clinical management and ultimate perinatal survival, normative growth curves for this high-risk group are particularly important. This proposed longitudinal reference combines both prenatal and postnatal measures, and corrects for ultrasonographic bias. The advantage of this reference is that it combines both in utero fetal weights and birth weights of a diverse sample of triplets. These weight percentiles should be viewed more as a reference than a standard because we did not limit our study population to those with optimal birth weights and gestations. This new reference demonstrates that although poorly grown triplets differ substantially from twins and singletons as early as 26 weeks' gestation, the overall pattern of fetal growth for well-grown triplets does not differ from that of singletons until 30 weeks and from that of twins until after 34 weeks. These data confirm in triplets what we have previously demonstrated in twins,[9] that, in utero, well-grown children have similar growth potentials, regardless of plurality.

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