Distortions in Fetal Growth Standards

RICHARD L. NAEYE⁽¹⁹⁾ AND JOSEPH B. DIXON

Department of Pathology and Research Computing Facility, M. S. Hershey Medical Center, The Pennsylvania State University College of Medicine, Hershey, Pennsylvania, USA

Summary

The study analyzed several errors incorporated in widely used fetal growth standards. Such standards contain measurements from many infants who died as neonates. The present study found many of these nonsurvivors to be growth retarded so new standards were developed which contain only measurements from survivors. The study also found that weights and other body measurements of prematurely born neonates cluster at intervals consistent with maternal vaginal bleeding at monthly intervals in early pregnancy. Such bleeding is often mistaken for the last menstrual period. To avoid this error, the probability plot method was used to separate the clusters of measurements at each gestational age. The cluster with the lowest values at each gestational age was used as the data base for the new growth standards. Standard deviations from most mean values in the new growth standards are much smaller than are such deviations in the older standards.

Speculation

At present there seems to be no completely valid method available to determine normal fetal growth using measurements from neonates because there is no assurance that prematurely born neonates are normally grown. Ultrasound and other modalities may eventually solve this problem by providing accurate, sequential *in utero* measurements of normal fetuses.

Fetal growth standards used throughout the world are based on body measurements of neonates born at various gestational ages. Standard deviations (SD) from mean birth weight values are relatively larger in preterm than in term infants in all of these older growth standards (1, 2, 4, 7, 8, 16). This raises the possibility that too many abnormally grown infants or those assigned inaccurate gestational ages have been included in the preterm standards because it is known that variations in fetal growth are

greater in late than in earlier gestation (5, 11, 12). The present study explored both the causes and possible remedies for these problems.

PATIENTS AND METHODS

The Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke provides a unique opportunity to study pregnancy and its outcome prospectively. It followed the course of pregnancies in 12 hospitals in various parts of the United States between 1959 and 1966 and recorded events of gestation, labor, delivery, and the neonatal period (14, 15). Measurements from 48,239 single born neonates were used in the analyses. All were alive and well at 1 year of age without disorders known to distort fetal growth. Such infants are subsequently termed "survivors." They included 24,698 males, 23,541 females, 22,286 blacks, 22,190 whites, and 3,763 of other racial and ethnic origins. There were great variations in the socioeconomic status of the infants' families (14).

Gestational ages were computed as the time between the first day of the last recorded menstrual period and the date of delivery, rounded to whole weeks. Some of these infants were older than their calculated gestational ages because monthly bleeding during early pregnancy is sometimes taken for the last menstrual period. Previous authors of fetal growth standards have used a variety of methods to exclude these infants who are older than their calculated gestational ages. Gruenwald used a bimodal curve in which he excluded the upper cluster, Lubchenco used a scattergram and review of clinical course, Babson and Brenner used the results of obstetric histories and maternal physical examinations, whereas Usher added clinical tests of the neonate's maturity to establish gestational ages (1, 2, 4, 8, 16). The present study attempted to develop a method for selecting infants to be included in fetal growth standards that was not dependent on case by case assessments of clinical findings.

Table 1. Birth weights in percentage of control values¹

	Gestational age at death (weeks)				No. of cases
	28-31	32-34	35-37	38-43	
Subgroup A					
Placenta previa	71 ± 23 ²	77 ± 11 ³		73 ± 31 ³	28
Abruptio placentae	86 ± 29 ⁴	89 ± 22 ⁴	84 ± 19 ⁴	89 ± 9 ⁴	136
Amniotic fluid infection syndrome	85 ± 22 ⁴	72 ± 35 ²	93 ± 21	90 ± 17	155
Premature rupture of membranes	96 ± 35	98 ± 21	82 ± 17 ²	92 ± 25	127
Umbilical cord knots	79 ± 25 ²	63 ± 19 ³	76 ± 10 ³	86 ± 22	43
Fetal hypoxia of unknown cause	71 ± 27 ²	65 ± 14 ³	84 ± 27 ⁴	85 ± 23	173
Subgroup B: Birth trauma	106 ± 16		98 ± 18	104 ± 19	21
Controls	100 ± 8	100 ± 9	100 ± 10	100 ± 11	48,289

¹ Nonsurviving infants with disorders that existed before the onset of labor (subgroup A) had undergrown bodies by comparison with liveborn infants who survived, *i.e.*, control infants. By contrast, infants who died as the consequence of birth trauma (subgroup B) had body measurements close to those of the surviving control infants. All values are ± 1 SD. Student's *t*-test was used to evaluate statistical significance.

² *P* < 0.02 compared with control group.

³ *P* < 0.005 compared with control group.

⁴ *P* < 0.05 compared with control group.

At each gestational age calculated from menses the number of cases was plotted at 20-g intervals of body weight. Before 38 weeks of gestation, cases were found to cluster at birth weight intervals consistent with vaginal bleeding at monthly intervals during early pregnancy. At each gestational age, the lowest weight cluster was used as the data base for that gestational age on the assumption that this cluster represented cases without pregnancy bleeding. The mean and SD for each cluster were determined by the probability plot method (3, 6). The same method was used to determine standards for placental weight, body length, and head circumference at each gestational age. Body and placental measurements from neonates born 38 weeks or more after the last recorded menstrual period were assumed to be correct and were used directly as the data base for the growth standards at those ages.

Published growth standards include measurements from infants who died as neonates. An effort was made to determine whether the inclusion of such cases distorts fetal growth standards. We compared fetal growth established for survivors by the cluster method with the growth of two subgroups who died as neonates. These two subgroups were selected because cases like them were likely included in previous growth standards. Subgroup A in-

Table 2. *Fetal body weight percentiles from 28 weeks of gestation to term based on birth weights of infants who survived*

Gestational age (weeks)	Body weight (g)					No. of cases
	10th ¹	25th ¹	50th ¹	75th ¹	90th ¹	
28	967	1085	1165	1245	1363	29
29	1124	1226	1295	1364	1466	42
30	1232	1356	1440	1524	1648	68
31	1386	1515	1601	1687	1816	111
32	1534	1675	1769	1863	2004	223
33	1703	1854	1955	2056	2207	303
34	1791	2012	2160	2308	2529	597
35	2008	2235	2387	2539	2766	1033
36	2121	2420	2621	2822	3121	1208
37	2354	2667	2878	3089	3402	2305
38	2570	2898	3119	3340	3668	4376
39	2676	3039	3283	3527	3890	9317
40	2776	3143	3388	3633	4000	11543
41	2778	3190	3466	3742	4154	9378
42	2778	3209	3498	3787	4218	5625
43	2780	3210	3499	3788	4218	2081

¹ Percentile.

Table 3. *Fetal body length percentiles from 28 weeks of gestation to term based on birth measurements of infants who survived*

Gestational age (weeks)	Crown heel length (cm)				
	10th ¹	25th ¹	50th ¹	75th ¹	90th ¹
28	36.2	37.3	38.0	38.7	39.8
29	37.3	38.3	39.0	39.7	40.7
30	38.7	39.7	40.3	40.9	41.9
31	39.4	40.6	41.4	42.2	43.4
32	40.6	41.7	42.5	43.3	44.4
33	41.8	43.1	43.9	44.7	46.0
34	42.8	44.3	45.3	46.3	47.8
35	44.0	45.6	46.7	47.8	49.4
36	45.2	46.9	48.0	49.1	50.8
37	46.1	47.8	48.9	50.0	51.7
38	46.7	48.5	49.7	50.9	52.7
39	47.0	48.8	50.0	51.2	53.0
40	47.1	49.1	50.4	51.7	53.7
41	47.1	49.3	50.7	52.1	54.3
42	47.1	49.3	50.8	52.3	54.5
43	47.2	49.4	50.9	52.4	54.6

¹ Percentile.

Table 4. *Fetal head circumference percentiles from 28 weeks of gestation to term based on birth measurements of infants who survived*

Gestational age (weeks)	Head circumference (cm)				
	10th ¹	25th ¹	50th ¹	75th ¹	90th ¹
28	24.4	25.3	26.0	26.7	27.6
29	25.4	26.3	26.9	27.5	28.4
30	26.5	27.3	27.9	28.5	29.3
31	27.1	28.0	28.6	29.2	30.1
32	28.0	28.8	29.3	29.8	30.6
33	28.8	29.6	30.1	30.6	31.4
34	29.4	30.2	30.8	31.4	32.2
35	30.2	31.0	31.6	32.2	33.0
36	30.8	31.8	32.4	33.0	34.0
37	31.4	32.4	33.1	33.8	34.8
38	31.8	32.9	33.6	34.3	35.4
39	31.9	33.0	33.8	34.6	35.7
40	32.0	33.3	34.1	34.9	36.2
41	32.0	33.3	34.2	35.1	36.4
42	32.0	33.4	34.3	35.2	36.6
43	32.1	33.4	34.3	35.2	36.5

¹ Percentile.

Table 5. *Fetal placental weight percentiles from 28 weeks of gestation to term based on cases in which infants survived*

Gestational age (weeks)	Placental weights (g)				
	10th ¹	25th ¹	50th ¹	75th ¹	90th ¹
28	217	242	259	276	301
29	232	257	273	289	314
30	236	265	284	303	332
31	243	278	301	324	359
32	262	296	319	342	376
33	274	311	336	361	398
34	282	324	353	382	424
35	289	336	368	400	447
36	288	347	387	427	486
37	297	364	409	454	521
38	304	377	426	475	548
39	304	383	436	489	568
40	305	387	442	497	579
41	306	393	451	509	596
42	306	396	457	518	608
43	307	398	459	520	611

¹ Percentile.

cluded infants with common fetal disorders not previously known to be associated with intrauterine growth retardation, *i.e.*, bacterial infections of the amniotic fluid, abruptio placentae, premature rupture of the membranes, placenta previa, umbilical cord knots, and fetal hypoxia of unknown cause. The numerically much smaller subgroup B included infants who died as a consequence of intrapartum trauma, mainly tentorial tears. Criteria for all these diagnoses have been previously published (9). The two subgroups constitute about 55% of all liveborn infants who subsequently died within the first month of life (9). The other 45% of nonsurvivors have diagnoses well known to be often associated with abnormal fetal growth, *i.e.*, major congenital malformations, Rh erythroblastosis fetalis, large placental infarcts, congenital rubella, syphilis, cytomegalovirus disease and several other disorders (9).

Neonates in subgroup A had undergrown bodies by comparison with the survivors, particularly at the earlier gestational ages (Table 1). By contrast, infants who died as the consequence of intrapartum trauma (subgroup B) had body measurements very close to those for the surviving control infants (Table 1). As subgroup A is much larger than subgroup B, it seemed wise to exclude all nonsurvivors from fetal growth standards and we did so for the current standards.

Fig. 1. Fetal body weight percentiles from 28–43 weeks of gestation.

Fig. 3. Fetal head circumference percentiles from 28–43 weeks of gestation.

Fig. 2. Fetal body length percentiles from 28–43 weeks of gestation.

Fig. 4. Placental weight percentiles from 28–43 weeks of gestation. In most cases, blood was allowed to drain from the organ and clots were removed before weights were taken.

RESULTS

The new fetal growth standards are found in Tables 2–5 and Figures 1–4. They include data from single, liveborn infants who survived. All the values were established by the cluster, probability plot method (3, 6). Most SD from mean values are much smaller in these new standards than in both previously published standards and in standards that include all the current 48,239 single born survivors (Table 6). These differences between the new and older standards are greater before 38 weeks of gestation than at term.

Both the frequencies and the mortality rates for several common fetal disorders were determined by growth category. All single born infants in the study were included in these analyses. Acute inflammation of the subchorionic plate of the placenta, a marker for amniotic fluid bacterial infections, was somewhat more fre-

quent when preterm infants were undergrown than when they were larger for gestational age (Table 7) (9). Perinatal death due to the disorder was most frequent in the most undergrown infants. The perinatal mortality rates decreased markedly with each increase in fetal growth category using Lubchenco growth standards (Table 7). These changes between growth categories were less when the new fetal growth standards were used (Table 7). Results were similar for placenta previa and for abruptio placentae.

DISCUSSION

Findings in the present study indicate that published fetal growth standards are likely distorted by the inclusion of many growth-retarded fetuses and by cases in which monthly vaginal bleeding in early pregnancy is taken for the last menstrual period. Authors of previous growth standards have made efforts to exclude

Table 6. *Birth weights from six sources*¹

Nearest week of gestation	Mean birth wt (g) $\pm$ 1 SD					12 US cities (all cases)	12 US cities (cluster method)
	Denver	Baltimore	Montreal	Portland	Chapel Hill		
28	1150 $\pm$ 259	1050 $\pm$ 310	1113 $\pm$ 150	1172 $\pm$ 344	1150 $\pm$ 272	1964 $\pm$ 593	1165 $\pm$ 109
29	1270 $\pm$ 294	1200 $\pm$ 350	1228 $\pm$ 165	1322 $\pm$ 339	1310 $\pm$ 299	2043 $\pm$ 671	1295 $\pm$ 94
30	1395 $\pm$ 341	1380 $\pm$ 370	1373 $\pm$ 175	1529 $\pm$ 474	1460 $\pm$ 340	2023 $\pm$ 654	1440 $\pm$ 115
31	1540 $\pm$ 375	1560 $\pm$ 400	1540 $\pm$ 200	1757 $\pm$ 495	1630 $\pm$ 340	2025 $\pm$ 655	1601 $\pm$ 117
32	1715 $\pm$ 416	1750 $\pm$ 410	1727 $\pm$ 225	1881 $\pm$ 437	1810 $\pm$ 381	2206 $\pm$ 634	1760 $\pm$ 128
33	1920 $\pm$ 505	1950 $\pm$ 420	1900 $\pm$ 250	2158 $\pm$ 511	2010 $\pm$ 367	2347 $\pm$ 654	1955 $\pm$ 138
34	2200 $\pm$ 539	2170 $\pm$ 430	2113 $\pm$ 280	2340 $\pm$ 552	2220 $\pm$ 395	2552 $\pm$ 559	2160 $\pm$ 202
35	2485 $\pm$ 526	2390 $\pm$ 440	2347 $\pm$ 315	2518 $\pm$ 468	2430 $\pm$ 408	2741 $\pm$ 637	2387 $\pm$ 208
36	2710 $\pm$ 519	2610 $\pm$ 440	2589 $\pm$ 350	2749 $\pm$ 490	2650 $\pm$ 408	2917 $\pm$ 521	2621 $\pm$ 274
37	2900 $\pm$ 451	2830 $\pm$ 440	2868 $\pm$ 385	2989 $\pm$ 466	2870 $\pm$ 395	2995 $\pm$ 518	2878 $\pm$ 288
38	3030 $\pm$ 451	3050 $\pm$ 450	3133 $\pm$ 400	3185 $\pm$ 450	3030 $\pm$ 395	3070 $\pm$ 440	3119 $\pm$ 302
39	3140 $\pm$ 403	3210 $\pm$ 450	3360 $\pm$ 430	3333 $\pm$ 444	3170 $\pm$ 408	3210 $\pm$ 434	3210 $\pm$ 434
40	3230 $\pm$ 396	3280 $\pm$ 450	3480 $\pm$ 460	3462 $\pm$ 456	3280 $\pm$ 422	3351 $\pm$ 448	3351 $\pm$ 448
41	3290 $\pm$ 396	3350 $\pm$ 450	3567 $\pm$ 475	3569 $\pm$ 468	3360 $\pm$ 435	3444 $\pm$ 456	3444 $\pm$ 456
42	3300 $\pm$ 423	3400 $\pm$ 460	3513 $\pm$ 480	3637 $\pm$ 482	3410 $\pm$ 449	3486 $\pm$ 463	3486 $\pm$ 463
43		3410 $\pm$ 490	3416 $\pm$ 465	3660 $\pm$ 502	3420 $\pm$ 463	3473 $\pm$ 502	3473 $\pm$ 502

¹ The final two columns compare values from the present study, all cases vs. those selected by the cluster method.

Table 7. *Frequency and mortality from several common perinatal disorders by percentile birth weight category*¹

	Birth wt, percentile growth category			
	<10	10–24	25–90	>90
Amniotic fluid infection syndrome				
New growth standard (present study)				
Frequency of the disorder in %	15.1 ² (154)	11.9%(144)	11.0%(239)	10.4(441)
Perinatal mortality from disorder	123.4 ³ (19)	34.7(5)	37.7(9)	11.3 ⁴ (5)
Lubchenco growth standard				
Frequency of the disorder in %	15.6(86)	13.9(129)	12.8(449)	8.6 ⁵ (314)
Perinatal mortality from disorder	151.2 ⁵ (13)	46.5(6)	33.4(15)	6.4 ² (2)
Abruptio placentae				
New Growth Standard				
Frequency of the disorder in %	9.3 ⁵ (111)	7.2(97)	4.3(104)	2.4 ⁵ (129)
Perinatal mortality from disorder	252.3(28)	144.3(14)	144.2(15)	100.8(13)
Lubchenco Growth Standard				
Frequency of the disorder in %	9.5 ⁵ (65)	8.6 ⁵ (95)	4.8(202)	1.8 ⁵ (79)
Perinatal mortality from disorder	230.8(15)	210.5(20)	138.6(28)	88.6(7)
Placenta previa				
New Growth Standard				
Frequency of the disorder in %	2.5(29)	2.2(30)	2.6(61)	0.9 ⁵ (51)
Perinatal mortality from disorder	241.4 ² (7)	33.3(1)	32.8(2)	78.4(4)
Lubchenco Growth Standard				
Frequency of the disorder in %	1.8(13)	2.8(33)	2.2(95)	0.7 ⁵ (30)
Perinatal mortality from disorder	307.7 ² (4)	90.9(3)	63.2(6)	33.3(1)

¹ Number of cases are in parentheses. Perinatal mortality: deaths/1000 births.

² $P < 0.05$ compared with growth percentile category 25–90.

³ $P < 0.01$ compared with growth percentile category 25–90.

⁴ $P < 0.1$ compared with growth percentile category 25–90.

⁵ $P < 0.001$ compared with growth percentile category 25–90.

these latter infants on a case by case basis using clinical histories, results of maternal physical exams, and neonatal physical and neurologic scales of maturation. Such methods appear not to have been entirely successful because all the published standards yield SD from mean birth weight values that are relatively larger in preterm than in term infants. Uterine and placental disorders have long been known to exert their greatest effects on fetal growth late in gestation and we have recently found that maternal calorie intake exerts its greatest influence on fetal growth late in gestation (5, 12, 13). Thus, variations in fetal growth are greatest near term so relative values for SD from mean birth weight values should progressively increase rather than decrease near term. The cluster method used to construct fetal growth standard in the present study yielded values for SD that are relatively larger in term than in preterm infants.

Changes in perinatal mortality rates between growth categories are less using the new growth standards than using the older ones (Table 7). The frequency of amniotic fluid infections is more closely related to qualitative aspects of maternal diets than to calorie intake and fetal growth. Thus, perinatal mortality rates due to the infections are about the same in dizygous twins and in the single born despite the much higher frequency of growth retardation in the twins (10, 11). Nearly complete studies in South Africa show that normal maternal calorie intake during pregnancy and consequent normal fetal growth are no protection against high death rates from the infections when maternal diets are deficient in specific constituents needed to maintain normal antimicrobial activity in the amniotic fluid (13). Thus, the known biology of the disorder offers no basis for the greater differences in perinatal mortality found between growth categories in the older compared with the new growth standards.

The second type of error commonly incorporated into the older fetal growth standards was easily recognized in the present study but means for correcting it are not as satisfactory. Previously published fetal growth standards combine measurements from infants who died in the neonatal period with measurements from those who survived (1, 2, 4, 7, 16). The present study found that fetal growth values are significantly larger in preterm infants who survive than in those who die so the new growth standards were based on measurements from survivors. Despite the exclusions, the new growth standards probably retain measurements from a disproportionate number of growth-retarded neonates because most of the disorders responsible for preterm deliveries are associated with retarded fetal growth.

The present study does not call into question the clinical usefulness of the widely used, older fetal growth standards. Rather it points out that they likely include data from both growth-retarded neonates and from some neonates older than their calculated gestational ages. At present, there seems no completely valid method available for determining normal fetal growth standards if such standards must be based on measurements of prematurely born infants.

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19. Requests for reprints should be addressed to: Dr. Richard L. Naeye, Department of Pathology, M. S. Hershey Medical Center, Hershey, PA 17033 (USA).
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