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Birthweight with Gestation and Maternal Characteristics in Live Births and Stillbirths

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Key Words
Normal range · Birthweight percentiles · Small for gestation · Stillbirth · Pyramid of antenatal care

Abstract
Objective: To establish a normal range of birthweight with gestational age (GA) at delivery and examine the contribution of maternal characteristics in defining growth restriction in stillbirths. ***Methods:*** In 69,895 normal singleton pregnancies, regression analysis was used to determine the association of birthweight with GA and maternal characteristics. The proportion of 290 stillbirths classified as small for GA depending on inclusion or exclusion of maternal characteristics was determined. ***Results:*** In normal pregnancies, there was a polynomial association between birthweight and GA. Birthweight increased with maternal weight, height and parity and was lower in Africans and South Asians than in Caucasians. Birthweight for GA was reduced in antepartum stillbirths (n = 243; $p < 0.0001$) but not in intrapartum stillbirths (n = 47; p = 0.334). There was no significant difference in the proportion of antepartum stillbirths with birthweight below the 10th percentile when birthweight was corrected for GA only compared to correction for GA and maternal characteristics (53.1 vs. 54.3%). The birthweight was below the 10th percentile in 71.8% of antepartum stillbirths at <32 weeks' gestation, in 47.2% at 33–36 weeks and in 31.5% at ≥37 weeks. ***Conclusion:*** Correction of birthweight for maternal characteristics does not alter the proportion of stillbirths that are small for GA.

Introduction

Impaired placentation is associated with the development of preeclampsia, fetal growth restriction and stillbirth. In defining the contribution of fetal growth restriction to stillbirth and the consequent development of strategies for prevention of this pregnancy complication, it is essential to determine normal growth with gestational age (GA). Previous studies have reported that fetal growth is affected by several maternal characteristics, including racial origin, weight, height and parity [1–3]. However, it is uncertain whether correction of birthweight for GA by maternal characteristics improves the proportion of stillbirths that can be classified as growth restricted.

The aims of this study are firstly, to establish a normal range of birthweight with GA at delivery; secondly, to ex-

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amine the contribution of maternal characteristics to birthweight for GA, and thirdly, to compare the proportion of stillbirths that are classified as small for GA (SGA) depending on inclusion or exclusion of maternal characteristics in defining birthweight percentiles for GA.

Methods

The study population consisted of 75,397 singleton pregnancies from King's College Hospital, University College London Hospital and Medway Maritime Hospital Kent. All women attended for their routine first hospital visit in pregnancy at 11–13 weeks' gestation. In this visit, we recorded maternal characteristics, including age, racial origin (Caucasian, African, South Asian, East Asian or mixed), history of medical conditions, parity (number of previous pregnancies ending at or after 24 weeks) and measured weight in kg and height in cm. We also performed a transabdominal ultrasound scan to determine GA from the measurement of the fetal crown-rump length [4], to diagnose any major fetal abnormalities, and to measure fetal nuchal translucency thickness as part of combined testing with serum free β-human chorionic gonadotropin and pregnancy-associated plasma protein A in screening for aneuploidies [5]. Data on pregnancy outcome were collected from the hospital maternity records or their general medical practitioners. Written informed consent was obtained from the women agreeing to participate in a study on adverse pregnancy outcome, which was approved by the Ethics Committee of each participating hospital.

The inclusion criteria for establishment of a normal range of birthweight for GA were: firstly, delivery of live birth of phenotypically normal neonate at or after 24 weeks' gestation, secondly, no maternal pre-pregnancy hypertension or diabetes mellitus, and thirdly, no preeclampsia, gestational diabetes mellitus (GDM) or iatrogenic delivery for fetal growth restriction in the current pregnancy.

Stillbirths included both antepartum and intrapartum deaths of phenotypically normal neonates occurring at or after 24 weeks' gestation. Antepartum stillbirth was defined as fetal death before the onset of labor, and in such cases the diagnosis was essentially made by ultrasonography in women presenting with reduced or absent fetal movements. Intrapartum stillbirth was defined as fetal death after the onset of labor and before birth, and in these cases there was ultrasonographic or cardiotocographic evidence that the fetus was alive at the onset of labor. We included all cases irrespective of maternal pre-pregnancy disease or pregnancy complication.

In our hospitals, two ultrasound scans are performed routinely in all patients: one at 11–13 weeks' gestation and another at 20–23 weeks. Subsequent scans are carried out when there are clinical indications, including the suspicion of an SGA fetus. If such scans confirm the diagnosis of fetal growth restriction, based on a combination of biometry, amniotic fluid volume and fetal Doppler indices, iatrogenic delivery may be undertaken. The definition of preeclampsia was that of the International Society for the Study of Hypertension in Pregnancy [6]. In our hospitals, screening for GDM was based on a two-step approach. Random plasma glucose was measured at 24–28 weeks' gestation, and if the concentration was more than 6.7 mmol/l, an oral glucose tolerance test was carried out within the subsequent 2 weeks. The diagnosis of GDM was made if the fasting plasma glucose level was at least 6 mmol/l or the plasma glucose level 2 h after the oral administration of 75 g glucose was 7.8 mmol/l or more [7].

This study is part of a research program on the early prediction of pregnancy complications. In a previous publication of 33,602 pregnancies, we established a reference range of birthweight with GA at delivery [8]. In this study of 69,895 pregnancies, we have included the normal population from the previous study to establish a normal range of birthweight with GA at delivery.

Statistical Analysis

A normal range of birthweight for GA was established from the live births fulfilling the inclusion criteria. GA at delivery was centered by subtracting 40 from GA in weeks. Linear regression analysis was used to determine the association of birthweight with GA. The standard deviation (SD) was estimated by regressing the absolute residuals on the estimated mean birthweight [9], which was subsequently multiplied by $\sqrt{(\pi/2)}$ (1.253314) to calculate the fitted SD. The observed birthweight was then expressed as z-score (difference between observed and expected divided by fitted SD) and percentile corrected for GA. Regression analysis was used to examine the association between GA corrected birthweight z-scores and maternal weight, height, racial origin and parity. Maternal weight was centered by subtracting 69 kg and maternal height was centered by subtracting 164 cm. The observed birthweight was then expressed as z-score and percentile corrected for GA and maternal characteristics. Unpaired t test was used to compare the birthweight z-scores for GA with and without correction for maternal characteristics between the normal population and stillbirths. Regression analysis was used to examine the association between birthweight z-scores and GA in the outcome groups. The proportion of stillbirths with birthweight below the 5th, 10th and 20th percentiles for GA with and without correction for maternal characteristics was determined and compared by the χ^2 test. The detection rates and false-positive rates for stillbirth in screening by birthweight for GA with and without correction for maternal characteristics were determined by receiver operating characteristics curve (ROC), and the areas under the ROC were compared [10].

The statistical software package SPSS 20.0 (SPSS Inc., Chicago, Ill., USA) and Medcalc (Medcalc Software, Mariakerke, Belgium) were used for the data analyses.

Results

During the study period, first-trimester combined screening for aneuploidies was carried out in 79,694 singleton pregnancies. We excluded 4,297 (5.4%) cases because they had missing outcome data (n = 2,407), the pregnancies resulted in miscarriage before 24 weeks of gestation, they were terminated or they resulted in the birth of babies with major defects (n = 1,890). In the remaining 75,397 singleton pregnancies, there were 75,104 live births and 293 (0.4%) stillbirths. In three of the still-

Table 1. Characteristics in the study population

Variables	Live birth (n = 75,104)	Stillbirth (n = 290)	p value
Median maternal age, years	31.3 (26.8–35.2)	30.9 (25.5–36.2)	0.772
Median weight, kg	65.4 (59.0–75.4)	70.0 (60.0–81.5)	<0.0001*
Median height, cm	164 (160–168)	165 (159–167)	0.061
Racial origin			
Caucasian	56,965 (75.8)	180 (62.1)	<0.0001*
African	11,037 (14.7)	89 (30.7)	<0.0001*
South Asian	3,600 (4.8)	12 (4.1)	0.701
East Asian	1,776 (2.4)	3 (1.0)	0.195
Mixed	1,726 (2.3)	6 (2.1)	0.949
Parity			
Nulliparous	36,914 (49.2)	142 (49.0)	0.997
Parous	38,190 (50.8)	148 (51.0)	0.997
Cigarette smoker	7,528 (10.0)	42 (14.5)	0.020*
Assisted conception	2,749 (3.7)	18 (6.2)	0.015*
Pre-pregnancy medical conditions	1,310 (1.7)	23 (7.9)	<0.0001*
Chronic hypertension	830 (1.1)	16 (5.5)	<0.0001*
Diabetes mellitus	521 (0.7)	8 (2.8)	<0.0001*
Pregnancy complications	4,104 (5.5)	44 (15.2)	<0.0001*
Preeclampsia	1,656 (2.2)	42 (14.5)	<0.0001*
Gestational diabetes	1,353 (1.8)	2 (0.7)	0.230

Figures in parentheses indicate percentages or interquartile range. Comparisons between live births and stillbirths were by χ^2 or Fisher exact test for categorical variables and Mann-Whitney U test for continuous variables. * $p < 0.05$, significant.

births, the fetal death was the consequence of maternal death (car accident in two and eclampsia in one), and these were excluded from further analysis. In the remaining 290 stillbirths, fetal death was antepartum in 243 (83.8%) and intrapartum in 47 (16.2%).

In the establishment of the normal range of birthweight for GA, we included only 69,895 (93.1%) of the 75,104 live births, after exclusion of pregnancies because of maternal chronic hypertension (n = 830), diabetes mellitus (n = 521), preeclampsia (n = 1,656), GDM (n = 1,353), or iatrogenic delivery for fetal growth restriction (n = 1,352). We excluded 176 (28.5%) of the 618 pregnancies that delivered at <32 weeks, 783 (22.9%) of 3,425 at 32–36 weeks and 4,250 (6.0%) of 71,061 at ≥37 weeks.

The characteristics of the pregnancies with 75,104 live births and 290 stillbirths are presented in table 1. In the group with stillbirth, compared to those with live birth, there was a higher prevalence of women of African racial origin, cigarette smokers, those with chronic hypertension, diabetes mellitus, preeclampsia, those conceiving with assisted conception techniques, and the weight of the women was higher and the birthweight lower.

Normal Population

In the normal population of 69,895 live births, there was a significant polynomial association between neonatal birthweight and GA (fig. 1; table 2):

Estimated mean birthweight = $3{,}459.382 + 156.069 \times (GA - 40) - 11.784 \times (GA - 40)^2 - 0.674 \times (GA - 40)^3$; $R^2 = 0.350$, $p < 0.0001$.

Fitted SD = $\sqrt{(\pi/2)} \times [-22.903 + 0.151 \times$ (estimated mean birthweight) – 1.393e-05 × (estimated mean birthweight)^2].

Regression analysis demonstrated that GA-corrected birthweight z-scores increased with maternal weight ($p < 0.0001$), height ($p < 0.0001$) and parity ($p < 0.0001$), and were lower in women of African ($p < 0.0001$) and South Asian ($p < 0.0001$) racial origin than in Caucasians (table 3). The contributions of each maternal factor to birthweight in grams at 40 weeks' gestation are illustrated in table 3.

There was no significant difference in the proportion of live births with birthweight below the 5th, 10th and 20th percentiles when birthweight was corrected for GA only, compared to correction for GA and maternal characteristics (table 4).

Table 2. Normal range of birthweight with GA at delivery

Gestation week	Mean	Fitted SD	Percentile									
			1st	3rd	5th	10th	20th	80th	90th	95th	97th	99th
24	708.2	95.2	486.7	529.1	551.6	586.2	628.1	788.3	830.1	864.7	887.2	929.6
25	743.2	100.9	508.5	553.4	577.2	613.9	658.3	828.2	872.6	909.2	933.0	978.0
26	815.5	112.6	553.5	603.7	630.2	671.1	720.7	910.2	959.8	1,000.7	1,027.2	1,077.4
27	920.8	129.3	619.9	677.5	708.0	755.0	811.9	1,029.6	1,086.5	1,133.5	1,164.0	1,221.6
28	1,055.1	150.1	705.9	772.8	808.2	862.8	928.8	1,181.4	1,247.5	1,302.0	1,337.4	1,404.3
29	1,214.4	173.9	809.9	887.4	928.4	991.6	1,068.1	1,360.8	1,437.3	1,500.5	1,541.5	1,619.0
30	1,394.7	199.8	930.0	1,019.0	1,066.1	1,138.7	1,226.6	1,562.9	1,650.8	1,723.3	1,770.5	1,859.5
31	1,591.9	226.8	1,064.4	1,165.4	1,218.9	1,301.3	1,401.1	1,782.8	1,882.6	1,964.9	2,018.4	2,119.5
32	1,802.0	254.0	1,211.0	1,324.2	1,384.1	1,476.4	1,588.2	2,015.8	2,127.5	2,219.8	2,279.8	2,393.0
33	2,020.8	280.8	1,367.5	1,492.6	1,558.9	1,660.9	1,784.5	2,257.2	2,380.7	2,482.7	2,549.0	2,674.1
34	2,244.4	306.4	1,531.5	1,668.1	1,740.4	1,851.7	1,986.5	2,502.3	2,637.1	2,748.5	2,820.8	2,957.3
35	2,468.7	330.4	1,700.1	1,847.3	1,925.3	2,045.3	2,190.7	2,746.8	2,892.2	3,012.2	3,090.1	3,237.4
36	2,689.7	352.3	1,870.2	2,027.2	2,110.3	2,238.3	2,393.2	2,986.2	3,141.2	3,269.2	3,352.3	3,509.2
37	2,903.3	371.8	2,038.4	2,204.0	2,291.8	2,426.8	2,590.4	3,216.2	3,379.8	3,514.9	3,602.6	3,768.3
38	3,105.5	388.8	2,201.0	2,374.2	2,465.9	2,607.2	2,778.3	3,432.7	3,603.8	3,745.1	3,836.8	4,010.0
39	3,292.2	403.3	2,354.1	2,533.7	2,628.9	2,775.4	2,952.8	3,631.6	3,809.0	3,955.5	4,050.7	4,230.3
40	3,459.4	415.2	2,493.5	2,678.5	2,776.5	2,927.3	3,110.0	3,808.8	3,991.4	4,142.3	4,240.2	4,425.2
41	3,603.0	424.6	2,615.2	2,804.4	2,904.6	3,058.8	3,245.6	3,960.4	4,147.2	4,301.4	4,401.6	4,590.8
42	3,719.0	431.7	2,714.6	2,907.0	3,008.9	3,165.7	3,355.6	4,082.3	4,272.3	4,429.1	4,531.0	4,723.3
43	3,803.3	436.6	2,787.7	2,982.2	3,085.2	3,243.8	3,435.9	4,170.8	4,362.8	4,521.4	4,624.5	4,819.0

In figure 2a we compare the 5th, 50th and 95th percentiles of our normal population with those of a previous study in which birthweight was estimated by combining the weight of normal neonates at term with ultrasound-derived fetal growth charts for earlier gestations [11]. The values were similar.

Comparison of Birthweight Percentiles with Gestation in the Normal and Total Population

We used the same approach as described above for the normal population of 69,895 live births, to derive the regression equation and fitted SD of neonatal birthweight with GA for our total population of 75,104 live births. In figure 2b we compare the 5th, 50th and 95th percentiles of the normal and total populations. The 50th percentiles were similar for pregnancies at term, but at earlier gestations the values were lower for the total than in the normal population. The 5th percentile in the total population was lower than in the normal population and the difference was inversely related to GA.

Stillbirth

The birthweight of antepartum and intrapartum stillbirths is illustrated in figure 3. Compared to the normal

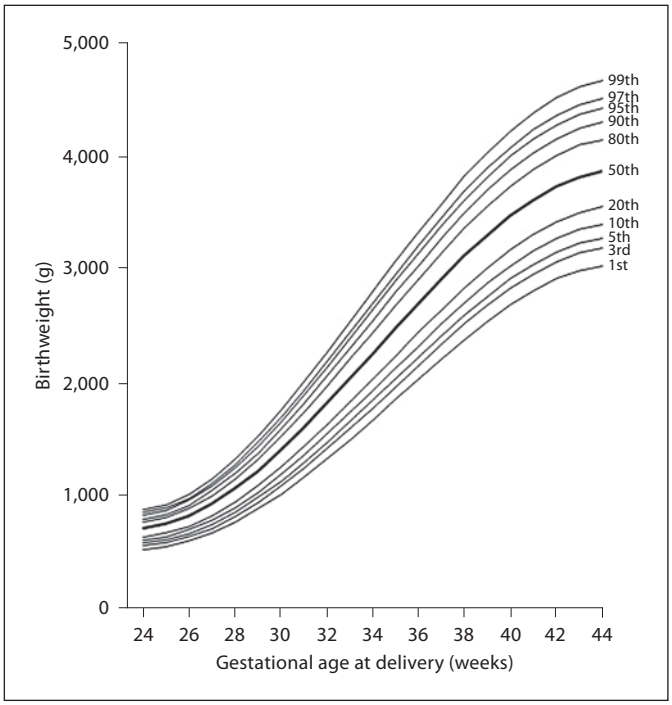

Fig. 1. The normal range of birthweight for GA at delivery.

Table 3. Association between birthweight z-scores corrected for GA and maternal characteristics

Estimated birthweight z-score	Maternal factors only			Contribution in grams at 40 weeks' gestation
	b	SE	p value	
Intercept	–0.032043	0.006016	<0.0001	
Weight – 69 kg	0.016188	0.000337	<0.0001	+5.358
(Weight – 69 kg)^2	–0.000160	0.000010	<0.0001	–0.053
Height – 164 cm	0.018545	0.000583	<0.0001	+6.138
Parity				
Nulliparous	0			
Para 1	0.255069	0.008184	<0.0001	+84.4
Para 2	0.265757	0.011865	<0.0001	+88.0
Para 3	0.259039	0.019338	<0.0001	+85.8
Para ≥4	0.213405	0.026473	<0.0001	+70.6
Racial origin				
Caucasian	0			
African	–0.332870	0.010715	<0.0001	–110.2
South Asian	–0.265004	0.017676	<0.0001	–87.8

Fitted SD = $(\pi/2) \times [0.745477 + 0.120971 \times (\text{estimated birthweight z-score}) + 0.087024 \times (\text{estimated birthweight z-score})^2]$.

Table 4. Proportion of live births with birthweight below the 5th, 10th and 20th percentiles for GA with and without correction for maternal characteristics in the total population and in normal pregnancies

Percentile	Total population (n = 75,104)			Normal pregnancies (n = 69,895)		
	correction for maternal factors			correction for maternal factors		
	no	yes	p value	no	yes	p value
<5th	4,131 (5.5)	4,265 (5.7)	0.130	2,977 (4.3)	3,071 (4.4)	0.222
<10th	8,146 (10.9)	8,187 (10.9)	0.740	6,410 (9.2)	6,486 (9.3)	0.488
<20th	16,293 (21.7)	16,184 (21.6)	0.498	14,002 (20.0)	13,905 (19.9)	0.521

Comparisons between birthweight correction for GA only vs. correction for GA and maternal characteristics were by χ^2 test.

population, the birthweight z-scores for GA with and without correction for maternal characteristics were significantly reduced in antepartum stillbirths (n = 243; p < 0.0001; p < 0.0001) but not in intrapartum stillbirths (n = 47; p = 0.334; p = 0.455; table 5). There was significant association between birthweight z-score with GA in antepartum stillbirths but not in intrapartum stillbirths (fig. 4).

There was no significant difference in the proportion of stillbirths with birthweight below the 5th, 10th and 20th percentiles when birthweight was corrected for GA only, compared to correction for GA and maternal characteristics (table 6).

The detection rates of stillbirth for false-positive rates of 5 and 10% in screening by birthweight corrected for GA were 35.9% (95% CI 30.3–41.7) and 44.5% (95% CI 38.7–50.4), respectively. The respective detection rates after correction of birthweight for maternal characteristics were 37.9% (95% CI 32.3–43.8) and 45.9% (95% CI 40.0–51.8). The area under the ROC for birthweight corrected for GA was not significantly improved by correction for maternal characteristics (0.712, 95% CI 0.709–0.715 vs. 0.716, 95% CI 0.713–0.719, p = 0.311).

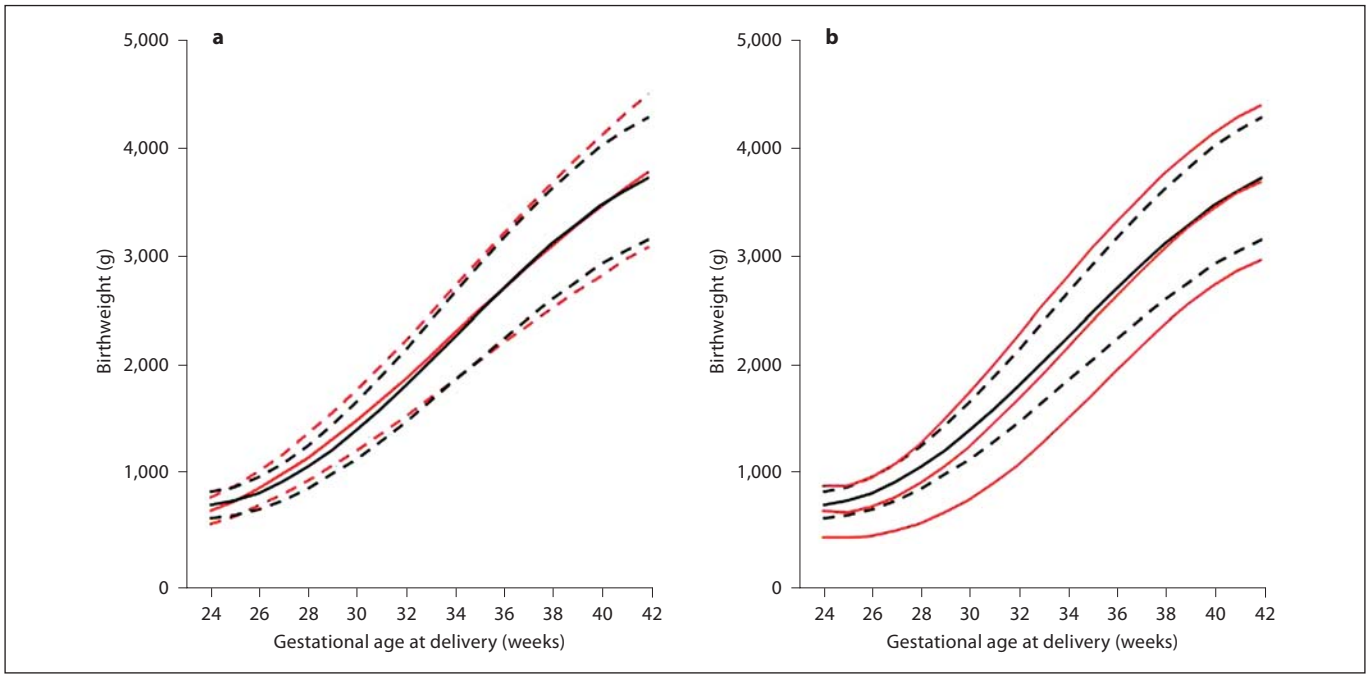

Fig. 2. The 5th, 50th and 95th percentiles of birthweight with GA in our normal population (black lines) and those of a previous study in which birthweight was estimated by combining the weight of normal neonates at term with ultrasound-derived fetal growth charts for earlier gestations (red lines; **a**) [10] and those in our total population (red lines; **b**). Colors refer to the online version only.

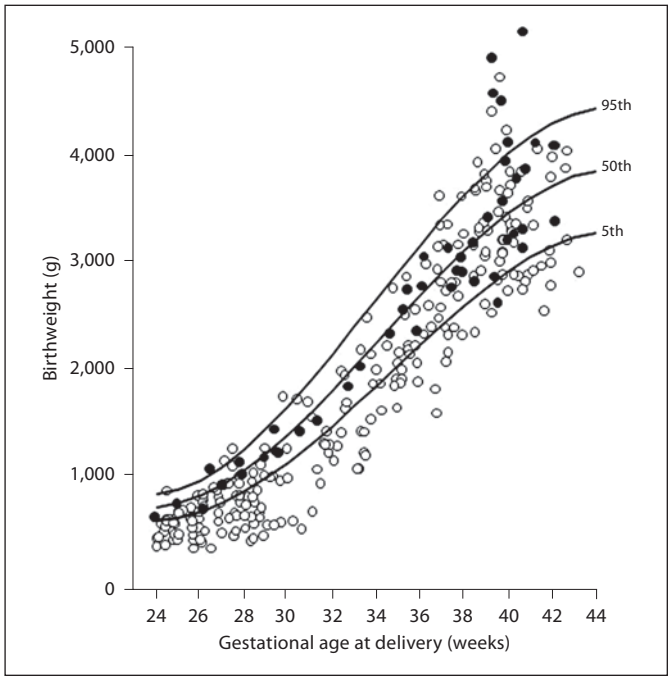

Fig. 3. Birthweight against GA at delivery in pregnancies complicated by antepartum stillbirth (open circles) and intrapartum stillbirth (solid dots), plotted on the 5th, 50th and 95th percentiles of the normal range.

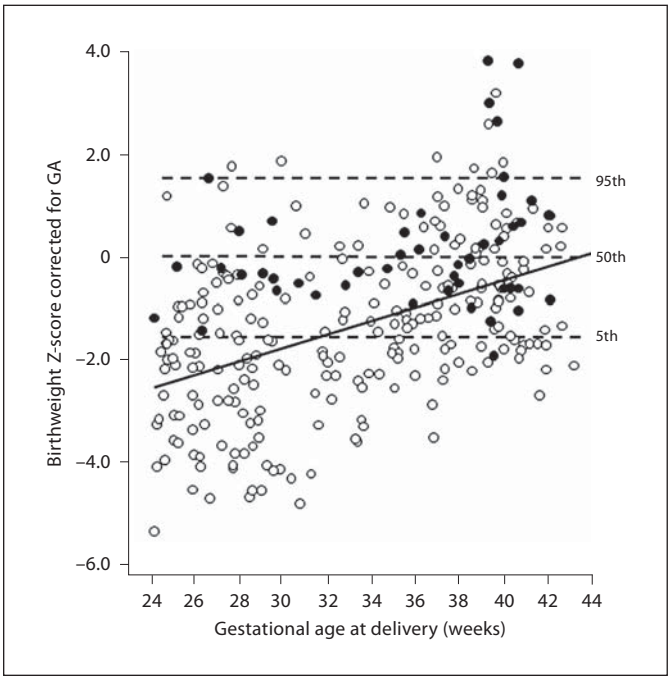

Fig. 4. Birthweight z-score corrected for GA at delivery in pregnancies complicated by antepartum stillbirth (open circles and solid regression line) and intrapartum stillbirth (solid dots), plotted on the 5th, 50th and 95th percentiles of the normal range.

Table 5. Mean and SD of birthweight z-score and Pearson correlation between birthweight z-score and GA at delivery in the live births and stillbirths

	Comparison with live births		Pearson correlation	
	mean ± SD	p value	r	p value
Live birth (n = 69,895)				
Birthweight z-score corrected for				
Gestational age only	0.000 ± 1.014	–	0.000	0.910
Maternal characteristics	0.002 ± 1.015	–	0.013	0.001
Total stillbirth (n = 290)				
Birthweight z-score corrected for				
Gestational age only	–1.123 ± 1.646	<0.0001	0.467	<0.0001
Maternal characteristics	–1.184 ± 1.682	<0.0001	0.440	<0.0001
Antepartum stillbirth (n = 243)				
Birthweight z-score corrected for				
Gestational age only	–1.369 ± 1.602	<0.0001	0.471	<0.0001
Maternal characteristics	–1.432 ± 1.649	<0.0001	0.457	<0.0001
Intrapartum stillbirth (n = 47)				
Birthweight z-score corrected for				
Gestational age only	0.147 ± 1.245	0.334	0.257	0.081
Maternal characteristics	0.101 ± 1.208	0.455	0.102	0.496

Table 6. Proportion of stillbirths with birthweight below the 5th, 10th and 20th percentiles for GA with and without correction for maternal characteristics

Percentile	Total	Total stillbirth			Total	Antepartum stillbirth			Total	Intrapartum stillbirth		
		correction for maternal factors				correction for maternal factors				correction for maternal factors		
		no	yes	p value		no	yes	p value		no	yes	p value
<5th												
Total	290	108 (37.2)	113 (39.0)	0.732	243	107 (44.0)	112 (46.1)	0.715	47	1 (2.1)	1 (2.1)	1.000
<32 weeks	123	69 (56.1)	74 (60.2)	0.605	110	69 (62.7)	74 (67.3)	0.572	13	0 (0.0)	0 (0.0)	–
32–36 weeks	61	20 (33.3)	21 (34.4)	0.848	53	20 (37.7)	21 (39.6)	0.842	8	0 (0.0)	0 (0.0)	–
≥37 weeks	106	19 (18.4)	18 (17.0)	0.856	80	18 (22.5)	17 (21.3)	0.848	26	1 (3.8)	1 (3.8)	1.000
<10th												
Total	290	131 (45.2)	135 (46.6)	0.803	243	129 (53.1)	132 (54.3)	0.860	47	2 (4.3)	3 (6.4)	0.646
<32 weeks	123	80 (65.0)	80 (65.0)	1.000	110	79 (71.8)	79 (71.8)	1.000	13	1 (7.7)	1 (7.7)	1.000
32–36 weeks	61	25 (41.0)	30 (49.2)	0.467	53	25 (47.2)	30 (56.6)	0.437	8	0 (0.0)	0 (0.0)	–
≥37 weeks	106	26 (24.5)	25 (23.6)	0.872	80	25 (31.3)	23 (28.8)	0.863	26	1 (3.8)	2 (7.7)	0.552
<20th												
Total	290	162 (55.9)	164 (56.6)	0.883	243	155 (63.8)	153 (63.0)	0.925	47	7 (14.9)	11 (23.4)	0.432
<32 weeks	123	91 (74.0)	86 (69.9)	0.570	110	89 (80.9)	85 (77.3)	0.619	13	2 (15.4)	1 (7.7)	0.539
32–36 weeks	61	37 (60.7)	37 (60.7)	1.000	53	36 (67.9)	35 (66.0)	0.836	8	1 (12.5)	2 (25.0)	0.522
≥37 weeks	106	34 (32.1)	41 (38.7)	0.389	80	30 (37.5)	33 (41.3)	0.746	26	4 (15.4)	8 (30.8)	0.323

Comparisons between birthweight correction for GA only vs. correction for GA and maternal characteristics were by χ^2 test.

Discussion

This study has established a normal range of birthweight for GA at delivery in a large heterogeneous inner-city unselected population of singleton pregnancies in which GA was determined by an ultrasound scan in early pregnancy. Birthweight increases with maternal weight, height and parity and is lower in women of African and South Asian racial origin than in Caucasians. In stillbirths, birthweight for GA is lower than in live births, but the proportion of stillbirths that are SGA is not altered by correction of birthweight for maternal characteristics.

Normal Range of Birthweight for GA

In the establishment of a normal range of birthweight for GA, we excluded pregnancies of women with chronic hypertension and diabetes mellitus and those complicated by fetal abnormalities, preeclampsia, GDM and severe fetal growth restriction requiring iatrogenic delivery. The association between these maternal and pregnancy conditions with abnormal fetal growth is well described [12–15], and in previous studies reporting on normal ranges these conditions have also been excluded [1–3]. This is particularly important for early gestations because a high proportion of pregnancies resulting in preterm birth are pathological. As illustrated in our study, exclusion of pathological pregnancies has a major impact on birthweight percentiles, which is particularly marked for preterm deliveries (fig. 2b).

Our study has demonstrated that by selecting a normal population, the median and SD of birthweight for GA and the effects of certain maternal characteristics are similar to those estimated in previous studies which combined data from normal pregnancies at term with ultrasonographically derived fetal growth charts [1–3].

Stillbirth Prevalence and Risk Factors

The rate of stillbirth in this study was 0.4%, which is comparable to the UK national rate of 0.47% in 2009 [16]. In our study, 16% of the stillbirths were intrapartum. The reported relative proportion of intrapartum to antepartum stillbirth increases with the overall rate of stillbirth [17]. The estimated proportion of intrapartum stillbirths worldwide is 45%, and this increases with the overall rate of stillbirth from about 14% for developed countries, where the stillbirth rate is about 3 per 1,000 births, to 57% in South Asia, where the stillbirth rate is 267 per 1,000 births [17].

The study has confirmed the known associations between certain maternal characteristics and increased risk for stillbirth, including African racial origin, high maternal weight, cigarette smoking, assisted conception, chronic hypertension, diabetes mellitus and preeclampsia. Large population-based studies reported that the risk of stillbirth is twice as high in African women, compared to Caucasians [16, 18], the risk increases with maternal weight [19–21], and it is higher in smokers than non-smokers [22] and in pregnancies conceived by in vitro fertilization and ovulation induction than in spontaneous conceptions [23]. A systematic review examining the causes of stillbirth reported that chronic hypertension is associated with an increased risk with odds ratios of 1.5–2.7 [24]. Similarly, a UK national population-based cohort study of 2,359 pregnancies in women with diabetes mellitus reported a twofold increase in the risk of stillbirth compared to non-diabetic women [25]. A US population-based study reported that in pregnancies with preeclampsia the risk of stillbirth is increased by 70% [26].

Correction of Fetal Weight for Maternal Characteristics

The proportion of stillbirths that can be classified as SGA was not improved by adjusting for maternal characteristics the birthweight for GA percentiles. This finding is in apparent contradiction to the results of previous studies which reported that infants classified as SGA by customized versus population-based birthweight standards have higher relative risks of perinatal mortality and morbidity [27–30]. However, a critical appraisal of customized birthweight standards demonstrated that their apparent benefit in improving the prediction of adverse perinatal outcomes is derived from their incorporation of intrauterine-based reference values at preterm ages rather than their adjustment for maternal characteristics [31]. Our results are in agreement with this suggestion because if we had used the percentiles derived from our total rather than the normal population, many of the preterm stillbirths would not have been identified as being growth restricted.

In women of African racial origin, birthweight is significantly lower than in Caucasian women after adjustment for maternal weight, height and parity. It could therefore be assumed that it is physiological for this racial group to produce smaller babies than Caucasians. The alternative view is that in women of African origin living in England the delivery of smaller babies is a consequence of pathological influences that would be masked by customized birthweight percentiles. We have previously reported that in women of African racial origin, after adjustment for other demographic and pregnancy charac-

teristics, there is increased risk for several adverse pregnancy outcomes, including miscarriage, stillbirth, preeclampsia, fetal growth restriction and preterm birth [32–36]. In our population, 15% of women were of African racial origin, and this group contributed to 30% of the stillbirths.

Implications of Our Findings for Strategies of Prevention of Stillbirth

Any strategy aiming to reduce stillbirth in developed countries should primarily target antepartum deaths since these account for more than 80% of cases. Nevertheless, every effort should be made to also reduce intrapartum stillbirths particularly so because the majority is preventable by better obstetric care. The UK confidential enquiry on perinatal death has reported that a high proportion of intrapartum deaths were associated with avoidable factors [16].

In 45% of our antepartum stillbirths, the death occurred at less than 32 weeks' gestation, and in this group the birthweight was below the 10th percentile for GA in 72% of the cases. The combination of early gestation and low birthweight implies that in many of these cases fetal death may be unavoidable. When the diagnosis of early-onset severe fetal growth restriction is made prenatally, the attending obstetricians in consultation with the parents could decide to avoid iatrogenic delivery because of the perceived high risk of neonatal death or severe handicap in survivors. A strategy for avoidance of such early stillbirths should focus on the early identification of high-risk pregnancies and undertaking of the necessary measures to improve placentation [37]. Recent studies have demonstrated that algorithms combining maternal characteristics and biophysical and biochemical tests at 11–13 weeks could identify most pregnancies delivering preterm SGA neonates in the presence or absence of preeclampsia [34, 35]. Furthermore, evidence from meta-analyses of randomized studies utilizing the prophylactic use of low-dose aspirin in pregnancies at high risk of preeclampsia reported that such therapy initiated before 16 weeks' gestation can substantially reduce preeclampsia, fetal growth restriction and perinatal death [38, 39].

In 55% of our antepartum stillbirths, fetal death occurred at ≥32 weeks' gestation, and in this group the birthweight was below the 10th percentile for GA in 38% of the cases. In this group, stillbirth could have been avoided by iatrogenic delivery, and failure to do so reflects the inadequacy of current antenatal care in the detection of severe fetal growth restriction. In the UK, ultrasound examination in the third trimester is not performed routinely, and the extent to which such a scan, as well as the timing and content of the scan, will identify and prevent stillbirths merits investigation.

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