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Birth weight in live births and stillbirths

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KEYWORDS: birth-weight percentiles; INTERGROWTH-21st standard; normal range; pyramid of antenatal care; small-for-gestational age; stillbirth

ABSTRACT

Objective *To establish a normal range of birth weights for gestational age at delivery and to compare the proportion of live births and stillbirths that are classified as small-for-gestational age (SGA) according to our normal range* vs *that of the INTERGROWTH-21st standard.*

Methods *The study population comprised 113 019 live births and 437 (0.4%) stillbirths. The inclusion criterion for establishing a normal range of birth weights for gestational age was the live birth of a phenotypically normal neonate ≥ 24 weeks' gestation and the exclusion criteria were smoking and prepregnancy hypertension, diabetes mellitus, systemic lupus erythematosus or antiphospholipid syndrome, pre-eclampsia, gestational hypertension, gestational diabetes mellitus or iatrogenic preterm birth for fetal growth restriction in the current pregnancy. Inclusion criteria were met by 92 018 live births. The proportions of live births and stillbirths with birth weights < 5th and < 10th percentiles of our normal range and those according to the INTERGROWTH-21st standard were determined and compared by the chi-square test and McNemar test.*

Results *The proportions of live births and stillbirths with a birth weight < 5th percentile according to our standard were significantly higher than and discordant with the proportion according to the INTERGROWTH-21st standard (live birth: 5.6%* vs *3.4%; stillbirth: 37.2%* vs *22.7%). Similarly, the proportion of live births and stillbirths with a birth weight < 10th percentile according to our standard were significantly higher than and discordant with those according to the INTERGROWTH-21st standard (live birth: 11.2%* vs *6.9%; stillbirth: 44.3%* vs *32.6%).*

Conclusion *The INTERGROWTH-21st standard underestimates the proportion of SGA live births and stillbirths in our population. Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Small-for-gestational-age (SGA) fetuses are at increased risk of perinatal death and both short- and long-term morbidity. The rate of SGA depends on the standards that define the condition and several studies reported population-based reference ranges or normal ranges of birth weight for gestational age (GA). Recently, an attempt has been made to establish a standard growth chart that would be applicable to all populations worldwide. The INTERGROWTH-21st standard was derived from a cohort of 20 486 women delivering between 33 and 42 weeks' gestation and 408 delivering < 33 weeks at centers in eight countries who were considered to be of adequate health and nutritional status, were at low risk of intrauterine growth restriction and received evidence-based pregnancy care[1,2]. The authors wanted to extend into fetal life the objectives promoted by the World Health Organization of establishing multiethnic and multicountry standards that indicate how healthy children grow in an environment that allows them to achieve their full growth potential[3,4], and reported that, in women at low risk of fetal growth impairment, optimum infant size at birth was almost identical among the eight included countries[1,2].

The ability of the INTERGROWTH-21st standard to identify infants at risk of adverse outcomes has been challenged recently by the results of a study of 53 484 singleton non-anomalous neonates born at 33–42 weeks' gestation in a multiethnic population in New Zealand; the INTERGROWTH-21st standard, by comparison with the local charts, underestimated both the rate of SGA neonates (4.5% *vs* 11.6%) and a composite of adverse neonatal outcome (14.6% *vs* 26.6%)[5].

The objectives of this study were to establish a normal range of birth weights for GA at delivery in a multiethnic population of 113 456 women with a singleton pregnancy, residing in and around London, UK, and compare the proportion of live births and stillbirths that are classified as SGA according to our normal range *vs* the proportions when using the INTERGROWTH-21st standard.

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METHODS

The study population consisted of 113 456 singleton pregnancies from King's College Hospital, London, and Medway Maritime Hospital, Kent, between March 2006 and October 2015. All women attended for their first routine hospital visit in pregnancy at 11–13 weeks' gestation. In this visit, maternal characteristics and medical and obstetric history were recorded and maternal weight in kg and height in cm were measured. An ultrasound examination was performed to determine GA from the measurement of the fetal crown–rump length[6], 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 trisomies[7]. Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. 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 criterion for establishment of a normal range of birth weight was delivery of a live phenotypically normal neonate ≥ 24 weeks' gestation. Exclusion criteria were maternal smoking, prepregnancy hypertension, diabetes mellitus, systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS), pre-eclampsia[8], gestational hypertension[8], gestational diabetes mellitus[9] or iatrogenic preterm birth for SGA in the current pregnancy.

Stillbirths included both antepartum and intrapartum deaths of phenotypically normal neonates occurring ≥ 24 weeks' gestation. Antepartum stillbirth was defined as fetal death before the onset of labor, and in such cases the diagnosis was made essentially by ultrasound 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 of stillbirth irrespective of the presence of maternal prepregnancy disease or pregnancy complication.

Statistical analysis

A normal range of birth weights for GA was established from the live births that fulfilled the inclusion and exclusion criteria. GA at delivery in weeks was centered by subtracting 40 weeks from the value. Linear regression analysis was used to determine the association of birth weight with GA. The SD was estimated by regressing the absolute residuals on the estimated mean birth weight[10,11], which was subsequently multiplied by $\sqrt{(\pi/2)}(1.253314)$ to calculate the fitted SD. The observed birth weight was then expressed as a *Z*-score (difference between observed and expected values, divided by the fitted SD) and the percentile corrected for GA. The observed birth weight was also expressed as a percentile according to the INTERGROWTH-21st standard[1,2]. The proportions of live births and stillbirths with birth weight < 5th and < 10th percentiles for GA, according to our normal range and the INTERGROWTH-21st standard, were determined and compared using chi-squared and McNemar tests. The statistical software package SPSS 22.0 (SPSS Inc., Chicago, IL, USA) was used for the data analyses.

Effect of maternal characteristics on neonatal birth weight

Regression analysis was used to examine the association between GA-corrected birth-weight *Z*-scores and maternal characteristics and history in the total and normal populations of live births. The proportion of live births and stillbirths with birth weight < 5th and < 10th percentiles for GA with correction for maternal characteristics were calculated. These results are presented in Appendix S1 and Tables S1–S3.

RESULTS

In the study population, there were 113 019 live births and 437 (0.4%) stillbirths. Among pregnancies with stillbirth there was a higher prevalence of Afro-Caribbean women, cigarette smokers, women with chronic hypertension and pre-existing diabetes mellitus and a lower prevalence of Caucasian women, and their weight at booking was higher. In the index pregnancy, there was a higher prevalence of pre-eclampsia and low birth weight.

In the population of 92 018 (81.4%) live births that fulfilled the inclusion criteria from which the range of

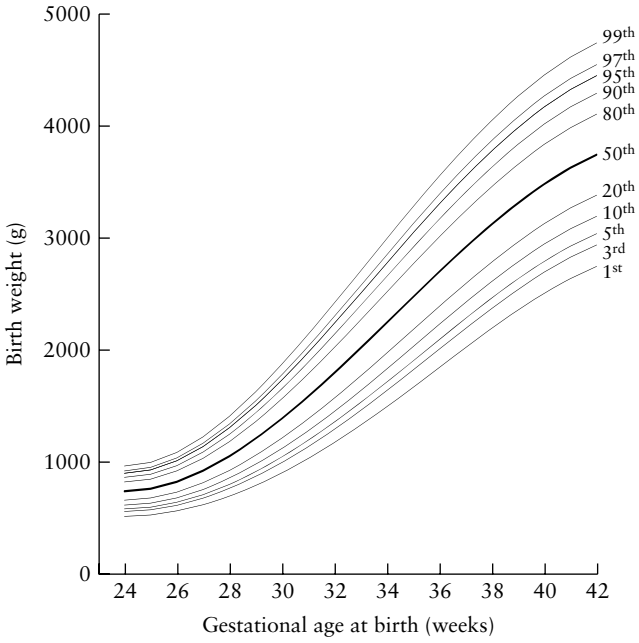

Figure 1 Normal range of birth weights for gestational age at delivery according to 92 018 singleton pregnancies with live birth.

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Table 1 Normal range of birth weights according to gestational age (GA) at delivery in 92 018 live births

GA at delivery (weeks)	n	Birth weight (g)													
		Observed mean	Observed SD	Estimated mean	Fitted SD	Percentile									
						1st	3rd	5th	10th	20th	80th	90th	95th	97th	99th
24	51	668	87	733	97	508	551	574	609	652	814	857	892	915	958
25	58	787	98	756	101	521	566	590	626	671	841	885	922	945	990
26	51	911	126	818	113	556	606	633	674	723	913	962	1003	1030	1080
27	47	1042	142	916	131	612	671	701	749	806	1026	1083	1131	1162	1220
28	72	1133	190	1045	153	689	757	793	849	916	1174	1242	1298	1334	1402
29	82	1312	202	1202	180	783	863	906	971	1050	1353	1432	1498	1540	1620
30	94	1454	217	1381	209	896	988	1038	1113	1205	1556	1648	1724	1773	1866
31	115	1665	232	1578	238	1024	1130	1186	1273	1378	1779	1884	1970	2026	2133
32	147	1839	285	1790	268	1167	1286	1349	1447	1564	2015	2133	2230	2294	2413
33	258	2128	312	2011	296	1322	1454	1524	1632	1762	2261	2391	2498	2568	2700
34	483	2318	329	2238	323	1488	1631	1707	1825	1967	2510	2652	2769	2845	2989
35	782	2564	370	2466	346	1660	1815	1896	2022	2175	2758	2910	3036	3118	3272
36	1617	2774	393	2691	367	1837	2001	2087	2221	2382	3001	3162	3296	3382	3546
37	4076	3012	429	2909	385	2014	2185	2276	2416	2585	3233	3403	3542	3633	3805
38	10 896	3220	425	3115	399	2187	2365	2459	2604	2779	3451	3627	3772	3866	4044
39	22 705	3386	418	3306	410	2351	2534	2631	2780	2960	3651	3832	3981	4078	4261
40	26 714	3530	421	3476	419	2501	2688	2787	2939	3123	3828	4012	4165	4263	4450
41	20 003	3671	433	3621	425	2633	2822	2922	3077	3264	3979	4166	4320	4420	4610
42	3624	3762	450	3738	429	2740	2931	3033	3188	3377	4099	4287	4443	4544	4736
43	143	3789	485	3821	431	2818	3010	3112	3269	3459	4184	4374	4531	4633	4825

normal birth weights for GA was established, there was a significant polynomial association between neonatal birth weight and GA:

Estimated mean birth weight $= 3475.715 + 158.472 \times (GA - 40) - 12.258 \times (GA - 40)^2 - 0.716 \times (GA - 40)^3$; $R^2 = 0.351$; $P < 0.0001$.

Fitted SD $= \sqrt{(\pi/2)} \times [-45.332 + 0.182 \times$ (estimated mean birth weight) $- 2.108 \times 10^{-5} \times$ (estimated mean birth weight)^2].

The normal range of birth weights corrected for GA at delivery is presented in Figure 1 and Table 1.

In 113 294 pregnancies, including 436 stillbirths, we compared our standard to that of the INTERGROWTH-21st, which is applicable only for deliveries up to 42 + 6 weeks' gestation (Figure 2 and Table 2). The 50th and 10th percentiles of the INTERGROWTH-21st standard are below the respective percentiles for our standard; the 90th percentile of the INTERGROWTH-21st standard is above our standard between 25 and 36 weeks' gestation and below our standard at term.

The proportion of live births and stillbirths with a birth weight < 5th percentile according to our standard (5.6% and 37.2%, respectively) were significantly higher than and discordant with those according to the INTERGROWTH-21st standard (3.4% and 22.7%, respectively). In cases of stillbirth, our normal range for birth weight detected 97/99 cases of SGA with a birth weight < 5th percentile classified by the INTERGROWTH-21st standard and detected 65 additional cases. The proportion of live births and stillbirths with a birth weight < 10th percentile according to our standard (11.2% and 44.3%, respectively) were significantly higher than and discordant with those according to

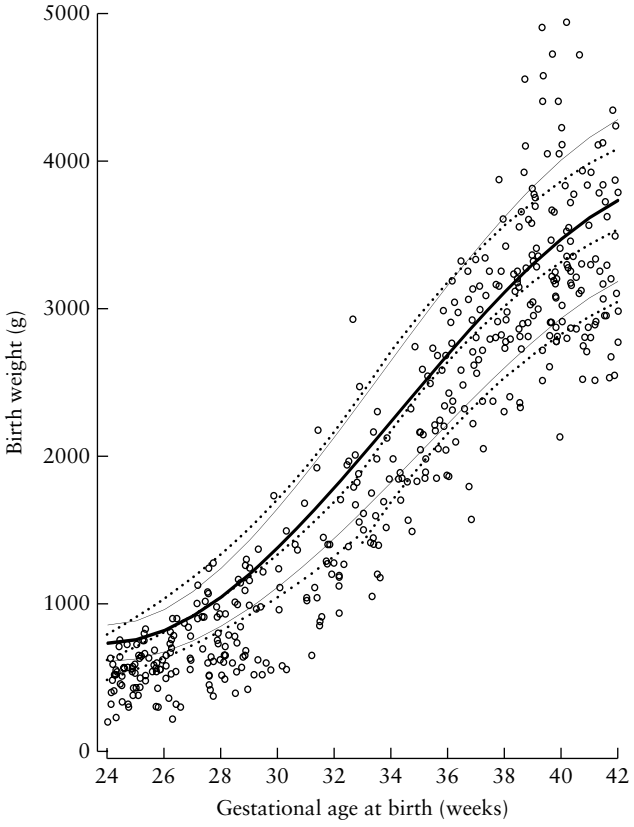

Figure 2 Birth weight according to gestational age at delivery in 436 pregnancies complicated by stillbirth, plotted against the 10th, 50th and 90th percentiles of our normal population (solid lines) and those of the INTERGROWTH-21st standard[1,2] (dotted lines).

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Table 2 Proportion of live births and stillbirths with birth weight < 5th and < 10th percentile for gestational age using normal growth range in present study, compared with those when using the INTERGROWTH-21st standard[1]

	Live birth			*Stillbirth*		
Cut-off	*Total*	*Present study*	*INTERGROWTH-21st*	*Total*	*Present study*	*INTERGROWTH-21st*
< 5th percentile						
All cases	112 858	6354 (5.6)	3846 (3.4)*†	436	162 (37.2)	99 (22.7)*†
Delivery < 32 weeks	997	147 (14.7)	113 (11.3)*†	174	104 (59.8)	61 (35.1)*†
Delivery 32–36 weeks	5371	648 (12.1)	489 (9.1)*†	94	31 (33.0)	22 (23.4)*†
Delivery ≥ 37 weeks	106 490	5559 (5.2)	3244 (3.0)*†	168	27 (16.1)	16 (9.5)*†
< 10th percentile						
All cases	112 858	12 627 (11.2)	7827 (6.9)*†	436	193 (44.3)	142 (32.6)*†
Delivery < 32 weeks	997	216 (21.7)	166 (16.6)*†	174	114 (65.5)	79 (45.4)*†
Delivery 32–36 weeks	5371	1033 (19.2)	799 (14.9)*†	94	40 (42.6)	35 (37.2)*
Delivery ≥ 37 weeks	106 490	11 378 (10.7)	6862 (6.4)*†	168	39 (23.2)	28 (16.7)*†

Data are given as *n* or *n* (%). Comparisons made between the standard in present study and that of INTERGROWTH-21st by chi-square test (*$P < 0.05$) and McNemar test (†$P < 0.05$).

the INTERGROWTH-21st standard (6.9% and 32.6%, respectively). In cases of stillbirth, our normal range detected 141/142 cases of SGA with a birth weight < 10th percentile classified by the INTERGROWTH-21st standard and detected 52 additional cases.

In order to detect 5% of SGA cases, the percentile according to the INTERGROWTH-21st standard is the 9.24th and the proportion of cases classified as SGA among stillbirths was 31.0% ($n = 135$), which was discordant but not significantly different when compared to the proportion of SGA classified by our standard (chi-square test: $P = 0.06$; McNemar test: $P < 0.0001$). Our normal range detected 125/135 cases of SGA with a birth weight < 9.24th percentile classified by the INTERGROWTH-21st standard and detected 37 additional cases. The percentile according to the INTERGROWTH-21st standard for detecting 10% of SGA cases is the 16.93th and the proportion of cases classified as SGA among stillbirths was 41.1% ($n = 179$), which was discordant but not significantly different when compared to the proportion of SGA classified by our standard (chi-square test: $P = 0.373$; McNemar test: $P = 0.024$). Our normal range detected 169/179 cases of SGA with a birth weight < 16.93th percentile classified by the INTERGROWTH-21st standard and detected 24 additional cases.

DISCUSSION

Main findings of the study

In a large multiethnic inner-city unselected population of singleton pregnancies in the UK, the proportion of pregnancies with a live birth or stillbirth classified as SGA according to a locally derived normal range of birth weights for GA at delivery is substantially higher than with the use of the INTERGROWTH-21st standard[1,2].

Strengths and limitations

For establishing the normal range of birth weights for GA at delivery, we excluded smokers, pregnant women with chronic hypertension and diabetes mellitus and those complicated by fetal abnormalities, pre-eclampsia, gestational hypertension, gestational diabetes mellitus and severe fetal growth restriction requiring iatrogenic preterm delivery. The association between these maternal and pregnancy conditions and abnormal fetal growth is well described and, in previous studies reporting on normal ranges for birth weight, these conditions have also been excluded[12–15]. In the construction of a normal range, exclusion of potentially pathological pregnancies is particularly important for early gestational ages because a high proportion of pregnancies resulting in preterm birth are pathological and their inclusion would have a major impact on birth-weight percentiles[15].

The normal range derived from our population is appropriate for studies on populations with similar demographic characteristics and cannot be claimed to represent a universally applicable international standard.

Comparison with previous studies

One of the most important objectives of prenatal care is the identification of pregnancies at high risk for stillbirth and the prevention of this adverse event. As demonstrated in this study, a high proportion of stillbirths are SGA. The rate of stillbirth in this study was 0.4%, which is comparable to the UK national rate of 0.46% in 2013[16]. The proportion of stillbirths that can be classified as SGA with birth weight < 5th or < 10th percentile were substantially lower when the INTERGROWTH-21st standard was used instead of our normal range. Another major study, from New Zealand, has also challenged the ability of the INTERGROWTH-21st standard to identify neonates with a composite of adverse neonatal outcome; the INTERGROWTH-21st standard, by comparison with the local charts, underestimated the rate of such adverse outcome[5].

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Our normal range of birth weight for GA was derived from the study of 92 018 live births, which was more than four times higher than the study population for the INTERGROWTH-21st standard[1]. Furthermore, the INTERGROWTH-21st standard for pregnancies at 24–32 weeks' gestation was derived from the study of 408 neonates[2], compared to 717 cases in our study.

Implications for clinical practice

The concepts that first, women of appropriate size who are healthy and receive good prenatal care will deliver babies that achieve their full growth potential, second, in such pregnancies the birth weight for GA at delivery is the same irrespective of the country of origin and, third, the growth charts can be used as an international gold standard, is attractive[1–4]. We agree that in the establishment of a normal range of birth weights for GA we should not customize for maternal size, parity and racial origin as these are known risk factors of stillbirth. We support the use of a universally applicable idealized growth chart in underdeveloped countries. In these countries there are high rates of malnutrition, social deprivation, poor health and stunting of growth in infancy; the use of such a chart will highlight that a high proportion of fetuses are SGA at increased risk of adverse perinatal outcome and hopefully stimulate the need for improved prepregnancy and prenatal care.

However, as demonstrated by this study and the one conducted in New Zealand[5], the INTERGROWTH-21st standard underestimates the rates of SGA, stillbirth and adverse neonatal outcome. Consequently, at least in some developed countries, and even in deprived areas, as in our inner-city London population, the use of the INTERGROWTH-21st standard, rather than standards derived from the study of local populations, will falsely reassure that fetal/neonatal growth is normal in many pregnancies that are at increased risk of adverse outcome, and consequently likely to lead to an increase, rather than decrease, in perinatal mortality and morbidity.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Appendix S1 Birth weight corrected for maternal characteristics

Table S1 Association between birth-weight *Z*-scores corrected for gestational age and maternal characteristics in the total population of live births

Table S2 Association between birth-weight Z-scores corrected for gestational age and maternal weight, height, racial origin and parity in the total population of live births

Table S3 Proportion of live births and stillbirths with birth weight < 5th and < 10th percentiles for gestational age, with and without correction for maternal factors

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