

OBSTETRICS

A customized standard to assess fetal growth in a US population

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OBJECTIVE: The objective of the study was to assess the factors that affect fetal growth and birthweight, and to derive coefficients for a customized growth chart applicable in an American population.

STUDY DESIGN: This was a prospective cohort study of 35,235 pregnancies. Coefficients for physiological and pathological variables were derived by backward multiple regression.

RESULTS: The expected birthweight at 40.0 weeks for a standard-size primiparous mother of European origin in an uncomplicated pregnancy was 3453.4 g, very similar to the standardized birthweight observed in other populations. Physiological coefficients were derived for maternal height, weight, parity, ethnic origin, and

sex of the baby. Smoking, history of preterm delivery, and hypertensive diseases in the current pregnancy all had negative effects on birthweight, whereas babies of diabetic mothers weighed more. Low as well as high body mass index was associated with birthweight deficit at term.

CONCLUSION: Coefficients that allow determination of the customized growth potential, individually adjusted and excluding known pathological factors, have been derived. Babies of obese mothers have an increased risk of not reaching their fetal growth potential.

Key words: birthweight, customized growth charts, fetal growth, growth potential

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Accurate assessment of intrauterine growth is an essential part of antenatal care and perinatal research. It requires a standard that can be individually adjusted or customized to reflect the growth potential of the fetus in each pregnancy.¹

To determine the customized growth potential, a predicted weight at term for a pregnancy in optimal conditions is firstly calculated, using adjustment coefficients derived from the local population.² Physiological or constitutional variables such as maternal size, parity and ethnic origin are adjusted for, whereas pathological factors such as smoking, hypertensive diseases and diabetes are ex-

★ EDITORS' CHOICE ★

cluded, even if they are known to be present, to set the expected standard so as to better recognize if fetal growth has been affected. The predicted "term optimal weight" is combined with a proportionality function derived from an ultrasound-based fetal weight curve to determine the optimal and normal range of fetal weight for each point in gestation.²

Such a customized standard has been found to improve the distinction between normal and abnormal growth and to enhance our understanding of the factors associated with fetal growth restriction.³⁻⁷ It is recommended by Royal College of Obstetricians and Gynaecologists Guidelines⁸ and is already in widespread use clinically and in ongoing research. There has recently been a call for customized growth charts to be adopted by obstetricians in the United States.⁹

Locally derived standards with appropriate coefficients for adjusting the expected term weight according to physiological variables have been published for maternity populations in the United Kingdom,² New Zealand,¹⁰ France,¹¹ Spain,¹² and Australia.¹³

The main purpose of this study was to derive coefficients that can be used to determine a customized fetal growth potential in an American population.

MATERIALS AND METHODS

Study population

Anonymized data were obtained from a National Institutes of Health-sponsored study conducted at 15 centers across the United States to evaluate screening tests in singleton pregnancies, conducted between October 1999 and December 2002 with institutional review board approval and participants' informed consent. All pregnancies were dated by ultrasound, and entry into the study was between gestational age of 10 weeks 3 days through 13 weeks 6 days according to fetal crown rump measurement. Details of the database have been described elsewhere.¹⁴ By agreement with the original study team, the data obtained for this study were analyzed by us independently.

Of a total of 38,033 cases, 2798 were excluded because of missing or inconsistent values for gestation and/or birthweight, leaving 35,235 cases for univariate analysis. To derive coefficients for customized centiles, a further 4398 cases

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TABLE 1
Characteristics of study population

Characteristic	n with data	n	%	Mean	SD	Median	IQR
Maternal age (y)	35,255	—	—	30.1	5.8	30.3	8.7
Maternal height (cm)	34,895	—	—	164.5	7.1	165.1	10.2
Maternal weight (kg)	35,228	—	—	67.6	14.9	64.1	15.9
BMI (kg/m ²)	34,871	—	—	25.0	5.2	23.7	6.0
< 20	—	3890	11.2	—	—	—	—
20-29.9	—	25,864	74.2	—	—	—	—
≥ 30	—	5117	14.7	—	—	—	—
≥ 35	—	1905	5.5	—	—	—	—
Parity	35,247	—	—	—	—	—	—
0	—	15,949	45.2	—	—	—	—
1	—	11,525	32.7	—	—	—	—
2	—	5084	14.4	—	—	—	—
3	—	1783	5.1	—	—	—	—
≥ 4	—	906	2.6	—	—	—	—
Ethnic origin	35,232	—	—	—	—	—	—
African American	—	1741	4.9	—	—	—	—
Asian/Pacific Islander	—	1391	3.9	—	—	—	—
European	—	23,898	67.8	—	—	—	—
Hispanic	—	7867	22.3	—	—	—	—
Native American/Alaskan	—	210	0.6	—	—	—	—
Other	—	125	0.4	—	—	—	—
Smoking (n/d)	35,224	—	—	—	—	—	—
1-9	—	1120	3.2	—	—	—	—
10-19	—	431	1.2	—	—	—	—
≥ 20	—	90	0.3	—	—	—	—
Alcohol (drinks/wk)	35,226	—	—	—	—	—	—
0.5-2	—	578	1.6	—	—	—	—
≥ 3	—	180	0.5	—	—	—	—
Marijuana use	35,243	325	0.9	—	—	—	—
Cocaine use	35,246	33	0.1	—	—	—	—
History of	—	—	—	—	—	—	—
Abortion	35,235	6083	17.3	—	—	—	—
Miscarriage	35,216	9207	26.1	—	—	—	—
Preterm birth	35,230	—	—	—	—	—	—
1	—	2023	5.7	—	—	—	—
2+	—	312	0.9	—	—	—	—
Diabetes	35,203	313	0.9	—	—	—	—
Gestational diabetes	35,135	1232	3.5	—	—	—	—

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(continued)

TABLE 1
Characteristics of study population (continued)

Characteristic	n with data	n	%	Mean	SD	Median	IQR
Antepartum hemorrhage	35,234	—	—	—	—	—	—
Spotting	—	4441	12.6	—	—	—	—
Bleeding	—	555	1.6	—	—	—	—
Placental abruption	35,151	247	0.7	—	—	—	—
Pregnancy induced hypertension	35,142	1590	4.5	—	—	—	—
Preeclampsia	35,145	829	2.4	—	—	—	—
Threatened preterm labor	35,148	1792	5.1	—	—	—	—
Premature delivery (< 37 wks)	35,235	2530	7.2	—	—	—	—
Gestation at delivery (d)	35,255	—	—	274.8	13.1	277.0	13.0
Birthweight (g)	35,255	—	—	3345.3	541.8	3373.7	630.5
Sex	35,202	—	—	—	—	—	—
Male	—	17,911	50.9	—	—	—	—
Female	—	17,291	49.1	—	—	—	—
Delivery mode	35,117	—	—	—	—	—	—
Vaginal unassisted	—	24,067	68.5	—	—	—	—
Vaginal operative	—	2639	7.5	—	—	—	—
Cesarean	—	8411	24.0	—	—	—	—
Stillbirth	35,235	70	0.2	—	—	—	—
Neonatal death	35,235	31	0.1	—	—	—	—

BMI, body mass index; IQR, interquartile range.

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were excluded, which consisted of preterm deliveries (< 37 weeks) and/or cases with an incomplete set of variables, resulting in 30,837 cases for the multiple regression analysis.

Statistical analysis

The covariates for the multiple regression model are listed in Table 1. They include physiological variables such as maternal height and weight, parity, ethnicity, and the sex of the baby; in addition, pathological factors were assessed, relating to past history or complications in the current pregnancy. Maternal characteristics such as weight and smoking status were collected at time of recruitment.

Coefficients for customized birthweight centiles were derived according to methods described previously,² using multiple regression with covariate selection by backward elimination and input and removal significance levels of 0.05. Both physiological and pathological variables were used to calculate the re-

spective coefficients. However, only the nonpathological variables are used in an additive model to adjust the predicted term weight and growth potential. In addition to maternal height and weight, we also included low and high body mass index (BMI) as pathological categories, based on less than the 10th and greater than the 90th centiles of the BMI distribution in this population (Table 2).

A standard ANOVA test yielded $P < .001$, giving the model as significant. Test of residuals confirmed assumptions of normality, linearity and uniformity of variance.

To allow comparison with previous studies,^{2,10,13} the birthweight constant was calculated for a gestation length of 280 days and a standard mother, defined as of Anglo-European origin, in her first pregnancy, height 163 cm, weight 64 kg, and the baby's sex unspecified or neutral.

All analyses were performed using either SPSS (version 14.0; SPSS Inc, Chi-

cago, IL) or Excel 2003 SP3 (Microsoft, Redmond, WA).

RESULTS

Table 1 describes the characteristics of the study population and lists the covariates entered into the multivariate model. The results of the multiple regression analysis are presented in Table 2, listing coefficients for the significant variables together with their standard error and P value. The overall R^2 of the model was 0.27. Maternal height, weight at first visit, parity, and the baby's sex were significant variables. For ethnic origin, only African American, Hispanic, and a miscellaneous "other" group reached significance.

Several pathological factors were significant, including past history and complications during the index pregnancy (Table 2). Both high and low BMI had a negative effect on birthweight, with high BMI the stronger factor.

TABLE 2
Coefficients from multiple regression model

Variable	Coefficient	SE	P value
Gestational age (from 280 d)			
Linear term	22.86	0.45	< .001
Quadratic term	-0.311	0.026	< .001
Cubic term	-0.007	0.002	< .001
Sex			
Male	66.0	2.2	< .001
Female	-66.0	2.2	< .001
Maternal height (from 163 cm)			
Linear	6.398	0.434	< .001
Cubic	-0.003	0.001	.0015
Maternal weight (from 64 kg)			
Linear	7.578	0.338	< .001
Quadratic	-0.087	0.015	< .001
Cubic	0.0005	0.0002	< .0041
Ethnic origin			
African American	-161.0	11.0	< .001
Hispanic	-38.6	5.7	< .001
Other	-140.8	39.6	< .001
Parity			
Para 1	96.2	5.2	< .001
Para 2	121.9	6.9	< .001
Para 3	125.9	10.7	< .001
Para ≥ 4	122.7	14.6	< .001
Past history			
Miscarriage	12.9	5.1	.0118
Preterm delivery 1	-55.1	10.4	< .001
Preterm delivery ≥ 2	-77.6	29.1	.0077
Smoking (n/d)			
1-9	-99.2	12.8	< .001
10-19	-174.9	20.2	< .001
≥ 20	-246.3	45.8	< .001
Low BMI (< 19.83 kg/m ²) ^a	-20.4	9.3	.0283
High BMI (> 31.71 kg/m ²) ^a	-63.4	12.4	< .001
Diabetes	241.7	26.1	< .001
Antepartum hemorrhage	-41.2	18.7	.0271
Pregnancy induced hypertension	-26.8	11.4	.0184
Preeclampsia	-60.7	18.3	< .001

Analysis centered on 280 days' gestation, for a standard mother (height 163 cm, weight 64 kg at first visit, para 0, European origin). Coefficients of model: constant, 3453.4g; SE, 382.6; R², 0.27.

BMI, body mass index, SE, standard error.

^a Limits represent 10th and 90th centiles for BMI in this population.

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In Table 3, the physiological coefficients for a standard mother are compared with previous analyses in England, New Zealand, and Australia^{2,10,13} and show close similarities, with no statistical difference in any of the categories with the exception of some variation in the higher parity groups. The constants (ie, the potential term birthweights for a standard mother) were also remarkably similar: 3453.4 g (United States), 3455.6 g (United Kingdom), 3464.4 g (New Zealand), and 3463.6 g (Australia).

COMMENT

This analysis shows that in an American population, birthweight varies with similar physiological factors to those found in maternity populations elsewhere,^{2,10,13} including maternal height, weight, parity, and ethnic origin as well as gestational age and sex of the baby. Furthermore, the magnitude of effect of these variables on birthweight is similar, suggesting that they apply universally. Once such variables are adjusted for, and pathological factors excluded, comparisons across geographical boundaries are possible. Our results show that populations of similar Anglo-European origin show striking similarities in the constant (ie, the birthweight expected for a standard size mother at the end of a normal pregnancy) (Table 3).

The standard mother principle allows interesting international comparisons of the effect of ethnicity on birthweight. In the current study, babies of African American mothers weigh 161.0 g less, which lies between the coefficients for African Caribbean (-127.5) and sub-Saharan African (-218.5g) ethnic groups in England.² Babies of Hispanic mothers were found to weigh 38.6 g less but neither of the other 2 ethnicities specified in this database, Asian and Native American, showed statistically significant differences. This could be a result of too few cases, heterogeneity, a weak effect on birthweight, or a combination of factors.

A recent study¹⁵ using the same database but different methodology found that babies of Asian mothers weigh 73.8 g less than the white (European) reference. However, this is likely to be a composite

figure of a heterogeneous Asian group. We know from other studies (Table 3) that south Asian babies can weigh up to 187 g less and Chinese babies 100 g more than their European counterparts.

Further work is needed to improve our understanding of the effect of ethnicity on birthweight. First, the database here was not large enough to assess growth in other ethnic groups living in America. Second, there are intergenerational differences, and the respective contributions of ethnicity and maternal size on increased birthweight in second or third generation migrants has yet to be quantified. Third, more information is required to study potential hidden confounders such as social deprivation that may affect fetal growth. However, differences in weight for gestation between ethnic groups persist when low-risk groups are compared, after exclusion of disproportionate social and other factors.¹⁶

The database provides information about several pathological factors (Table 2). Their effect on birthweight can be assessed better when physiological factors are also included in the multivariate analysis: this results in a predicted term weight that is free from such pathology and thus represents an optimal growth potential. Even though adverse factors such as past obstetric history or maternal smoking are known at the beginning of pregnancy, they are not used to calculate the term optimal weight (TOW) to which a baby is expected to grow: the aim of customized growth curves is not to predict the actual birthweight but to produce the optimal standard which is attainable, and against which the effects of any pathology can then be measured.

The adverse effect of smoking on fetal growth and birthweight is well known.¹⁷ The current analysis allows this effect to be quantified after adjustment for other maternal and pregnancy variables (Table 2). Comparison with other analyses using similar standardization and multiple regression techniques again shows remarkable similarities and demonstrates a dose-dependent deficit, which increases to about 250 g at term (current study: 246.3 g; England: 246.0 g²; Spain: 256.2 g.¹²

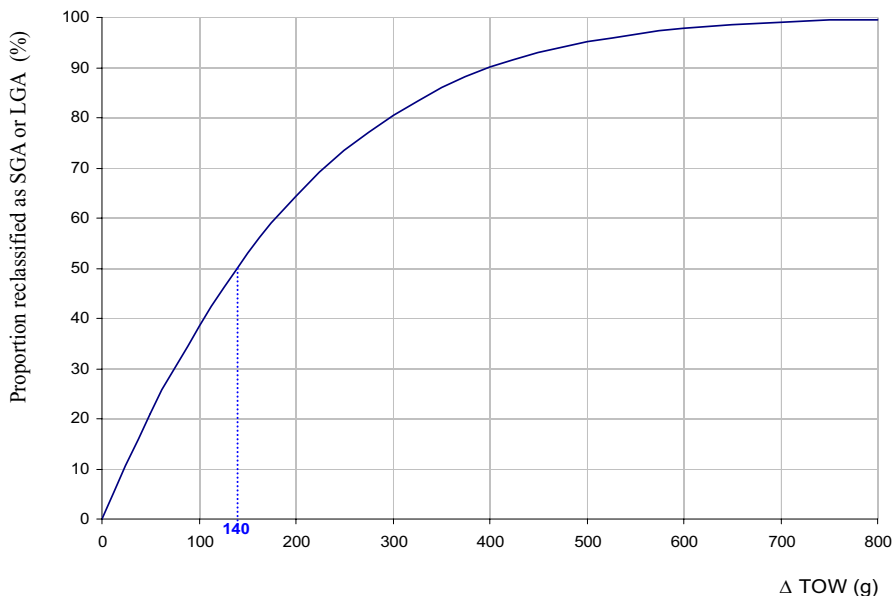
TABLE 3
Comparison of coefficients for standard mother

Variable	United States (current study)	England	New Zealand	Australia
Constant	3453.4	3455.6	3464.4	3463.6
SE of model	382.6	389.0	420.4	410.4
Gestational age (from 280 d)				
Linear term	22.86	20.7	19.5	19.1
Quadratic term	-0.311	-0.213	-0.28	-0.34
Cubic term	-0.007	-0.00017	0.0006	—
Sex				
Male	66.0	48.9	57.7	66.9
Female	-66.0	-48.9	-57.7	-66.9
Maternal height (from 163 cm)				
Linear	6.4	6.7	9.6	7.8
Cubic	-0.003	—	—	—
Maternal weight (from 64 kg)				
Linear	7.58	9.18	8.44	9.0
Quadratic	-0.087	-0.151	-0.114	-0.15
Cubic	0.0005	0.001	0.00065	0.001
Parity				
Para 1	96.2	101.9	101.6	94.8
Para 2	121.9	133.7	101.8	115.2
Para 3	125.9	140.2	123.3	116.0
Para ≥ 4	122.7	162.7	175.5	99.2
Ethnic origin				
African American	-161.0	—	—	—
African Caribbean	—	-127.5	—	—
African	—	-218.5	—	-297.4
Hispanic	-38.6	—	—	—
Middle Eastern	—	-89.9	—	-110.0
Bangladeshi	—	-79.3	—	—
Indian/Pakistani	—	—	—	-162.0
Indian	—	-149.4	-149.5	—
Pakistani	—	-187.3	—	—
Chinese	—	—	100.9	—
Maori	—	—	—	-66.8
Samoan	—	—	—	84.2
Tongan	—	—	—	124.1
Other	-140.8	—	—	—

Standard mother is defined as being of European origin, height 163 cm, weight 64 kg, first pregnancy, with baby sex averaged between male and female; current study compared with previous findings from England,² New Zealand,¹⁰ and Australia¹³. SE, standard error.

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FIGURE

Birthweights reclassified as SGA

Proportion of birthweights reclassified as SGA (less than the 10th centile) or LGA (greater than the 90th centile) because of adjustment of the term optimal weight (Δ TOW) in a standardised normal distribution with standard error 382.6 (Table 2). The example used in the text is marked (Δ TOW = 140 g).

LGA, large for gestational age; SGA, small for gestational age.

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The inclusion of high and low BMI in the multiple regression allowed us to assess the effect of pathological BMI in addition to the effect that maternal height and weight exert within normal BMI limits. Because BMI has been increasing in many societies in modern times, it is uncertain what the correct limits are today to distinguish normal from abnormal. Pragmatically, we used the 10th and 90th centiles for BMI in this population sample, which ensured that we had sufficient numbers in each category for the regression analysis. The results show first that mothers who have a low BMI and are potentially malnourished may have smaller babies, even after adjusting for maternal size and other constitutional variables, although the effect is relatively small (-20.4 g).

At the other end of the BMI spectrum, however, the finding of a more substantial, negative effect (-63.4 g) of obesity on birthweight seems at first surprising and contradicts previous observations that high maternal weight protects the baby from being small for gestational age

(SGA).¹⁸ However, we believe that this finding demonstrates the value of adjusting the definition of the SGA limit according to physiological variables, in order to better identify pathology. Recent preliminary analysis of a large Swedish database has shown that application of customized centiles in a population of large BMI mothers helps to identify a group of SGA babies not recognised by population centiles, which are at significantly increased risk of stillbirth.¹⁹

The more pathological factors are identified and recorded in a database, the more likely that a term optimal weight can be determined that is free from all such pathology. To test their effect, we ran the multiple regression without pathological variables and included physiological factors plus smoking only. This resulted in a minimal difference in the constant (the birthweight at term expected for a standard mother), from 3453.4 (Table 2) to 3452.4, and an SE of the model that increased slightly, from 382.6 to 385.0.

In practice, pathological factors may have negative or positive effects on birthweight that may balance out or, with the exception of smoking, do not occur frequently enough in an unselected population to affect the constant. It also suggests that physiological factors act on birthweight independently of pathology, and it is valid to compare databases, even though they contain pathological variables to a different degree (Table 3).

Despite adjustment for many factors shown to affect birthweight, the R^2 of the model seems modest at 0.27, consistent with other studies.¹⁰ The R^2 is 0.16 if only gestational age is adjusted and increases only slightly to 0.18 if fetal sex is added. Our model therefore represents an improvement in R^2 from 0.16 to 0.27 (ie, 68% increase) over the use of birthweight-for-gestational age centiles only.

The reason for the overall low correlation as expressed by R^2 may be because of other factors affecting birthweight that we do not know about. However, it would be difficult to imagine what additional physiological or pathological variables could raise the correlation and predictive value much higher. We suggest that it is more likely that birthweight, as other biological measures, is subject to considerable random variation, whereas only the systematic factors can be predicted in any population sample. This is consistent with the finding that the SE in our model, with all variables included, is 382.6 g (Table 2), smaller than if only gestational age is adjusted for (SE 410.5 g).

Whereas random variation relates generally to the whole birthweight distribution, it mostly affects values around the mean, where most measurements are, and where small differences have little clinical significance. A systematic shift, on the other hand, would be most notable at the extremes such as the 10th and 90th centile limits defining small and large for gestational age, respectively. The Figure shows the shift across these limits, which would result from variations in the expected mean birthweight in either direction, in a population with an SE of 382.6 g. For example, for a mother who is 10 cm taller and 10 kg heavier than average,

her BMI would still be normal, but the expected birthweight would be about $(10 \times 6.4 \text{ g}) + (10 \times 7.6 \text{ g}) = 140 \text{ g}$ heavier than that of a standard size mother (Table 2). According to the Figure, a 140 g shift would mean that 50% of babies who should be considered SGA would not be identified as such, if adjustment for maternal stature is not used.

In conclusion, analysis of the main physiological variables affecting fetal growth shows that they have a similar effect on normal fetal growth in this population as elsewhere, further adding to the concept that the best local and international standard for fetal growth is one that is individually adjustable. Larger multiethnic American databases will provide further opportunity to study the influences on birthweight in different parts of the population. In the meantime, the coefficients derived in this analysis have been added as an American version of the Gestation Related Optimal Weight (GROW) program (available for free download from www.gestation.net).²⁰ The program includes software to generate customized growth charts for individualized prediction of fetal growth potential for prospective surveillance, and a centile calculator for the retrospective assessment of birthweight. ■

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