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Customised birthweight standard for a Slovenian population

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Abstract

Objective: To produce a customised birthweight standard for Slovenia.

Methods: This retrospective study used a cohort from the National Perinatal Information System of Slovenia (NPIS). Prospectively collected information from pregnancies delivered in all of Slovenia's 14 maternal hospitals between 1st January 2003 and 31st December 2012 was included. Coefficients were derived using a backward stepwise multiple regression technique.

Results: A total of 126,627 consecutive deliveries with complete data were included in the multivariable analysis. Maternal height, weight in early pregnancy and parity as well as the baby's sex were identified as physiological variables, with coefficients comparable to findings in other countries. The expected 280-day birthweight, free from pathological influences, of a standard size mother (height 163 cm, weight 64 kg) in her first pregnancy was 3451.3 g. Pathological influences on birthweight within this population included low and high maternal age, low and high body mass index (BMI), smoking, pre-existing and gestational diabetes and pre-existing and gestational hypertension.

Conclusions: The analysis confirmed the main physiological variables that affect birthweight in studies from other countries, and was able to quantify additional pathological factors of maternal age and gestational diabetes. Development of a country-specific customised birthweight standard will aid clinicians in Slovenia with the distinction between normal and abnormal small-for-gestational age (SGA) fetuses, thus avoiding unnecessary interventions and improving identification of at risk pregnancies, and long-term outcomes for infants.

Keywords: birthweight; customised charts; fetal growth.

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Introduction

Intrauterine growth restriction and/or small-for-gestational age (SGA) babies are one of the major concerns and challenges in perinatal care. Growth restricted and/or SGA babies have an increased risk for perinatal morbidity and mortality, and once diagnosed, are more likely to lead to iatrogenic preterm birth, even with normal fetal investigations [1].

There are considerable inconsistencies in the definition, assessment and management of fetal growth restriction (FGR) in clinical practice [2]. Adjustment for physiological variables is thought to make assessment of fetal growth more precise and reduce unnecessary investigations, interventions and parental anxiety [3]. Large observational studies suggest that customised growth charts improve the differentiation between constitutional and pathological SGA neonates [3–7], which has shown to lead to improved detection of FGR and reduced false-positive diagnoses [8–10].

Implementation of customised growth at a population level has also been associated with increased antenatal detection of FGR and a decrease in stillbirth rates [11–13]. The Royal College of Obstetricians and Gynaecologists has recommended the use of a customised fetal weight reference when performing serial fetal growth measurements [14].

Customised charts adjust for physiological variables such as maternal weight and height, parity and ethnic origin that are known to influence birthweight and can be used to outline a customised growth curve for the expected fetal weight gain in each pregnancy. Coefficients of the significant variables that need to be adjusted for are derived statistically from local or national datasets and entered into a bespoke software programme.

In this study, we aimed to produce a customised birthweight standard based on the significant variables found in a Slovenian population.

Materials and methods

Data collection

We used anonymised aggregated data from the National Perinatal Information System of Slovenia (NPIS). The NPIS was started in 1987 and contains prospectively collected data on women, pregnancy, delivery, the postpartum period and the neonate for each mother-infant pair. The data are collected by the attending doctor and midwife as a part of a standardised medical system in all 14 maternal hospitals in Slovenia according to a standardised methodology and pre-defined set of variables [15]. Recording is mandated by law as the NPIS also serves as Slovenia's birth registry. Data are sent to the Slovenian National Institute of Public Health on a yearly basis where they undergo statistical quality checks, are edited and form the basis for the official perinatal Statistics of Slovenia. In the study period, 99.9% of women with singletons delivered in a hospital.

According to Slovenian law [16], the retrospective analyses of anonymised data sets are exempt from approval by Ethical Committee.

Inclusion/exclusion criteria

There were a total of 198,735 deliveries recorded from 1st January 2003 to 31st December 2012. We excluded 3491 multiple pregnancies, 1846 major fetal anomalies, 58,498 pregnancies with uncertain dates and 3688 pregnancies with missing data. Some women had more than one exclusion criterion. We were left with 134,425 singleton births with complete data on key variables (birthweight, gestational age, newborn sex, maternal height and weight, ethnic group and parity) for analysis.

Study population

Gestational age was assessed by the last menstrual period and ultrasound assessment in the first trimester. We excluded all pregnancies in which gestational age was uncertain. Maternal body height and pre-pregnancy weight were self-reported on the first prenatal visit. All citizens of Slovenia have regular periodical medical check-ups, including body height measurement, during primary school, high school, university and employment. All pregnant women are also weighed during regular prenatal visits including the first prenatal visit. Smoking was self-reported at the first prenatal visit and on admission to a delivery ward. Pre-existing diabetes (yes/no), gestational diabetes (yes/no) [15], pre-existing hypertension (yes/no) and gestational hypertension (yes/no) [17] were recorded on admission to a delivery ward. Data on body weight during pregnancy, gestational diabetes screening, blood pressure measurements and eventual proteinuria during pregnancy are documented in a maternity booklet which is a mandatory document for all pregnant women and checked on admission. Ethnicity was not included because more than 99% of this population are of Slovenian origin.

Statistical analysis

The covariates for the multiple regression are shown in Table 1. They include physiological variables such as maternal height and weight, parity and the sex of the baby and recorded pathological factors relating to past history or complications in the current pregnancy.

Coefficients for customised birthweight centiles were derived according to methods described previously [18]. Multivariate linear regression with stepwise backward elimination was used to obtain coefficients for significant variables with cut-off at a probability of 0.05. The regression analysis was run on a subset of 126,627 pregnancies, comprising live, singleton neonates free from major congenital abnormalities and delivery at term (37.0–42.0 weeks of gestation).

To allow comparison with previous studies [7, 19, 20], the analysis was centred on a standard mother with height 163 cm, booking weight 64 kg, gestation 280 days and parity zero and the baby's sex undefined, i.e. neutral or "averaged" between male and female. As maternal height and weight tend to have a non-linear relationship with birthweight, they were entered as polynomials up to the third power. Pathological factors were included as categorical variables to quantify their effect on birthweight but then excluded when calculating the "term optimal weight" free from pathology. All analyses were performed using Stata (version 15.1; Statacorp, College Station, TX, USA).

Results

The characteristics of the 134,525 pregnancies with complete data are listed in Table 1. Just under half were first pregnancies, 10.3% were smokers and 5.4% were born preterm.

The results of the multiple regression analysis run on the 126,627 pregnancies delivered at term are presented in Table 2, listing coefficients for the significant variables together with their standard error and P-value. The overall adjusted R^2 of the model was 0.263. The significant covariates used to model birthweight (in grams) were both physiological (gestational age, maternal height, weight, parity and the baby's sex) and pathological (maternal age, smoking, pre-existing and gestational diabetes and hypertension) as well as high and low body mass index (BMI) as derived variables. Categories of BMI, maternal age and smoking showed incremental, dose-response effects on birthweight (Table 2).

Applying the derived coefficients to the original dataset to calculate centiles resulted in an SGA (<10th centile) rate of 11.9 and a large-for-gestational age (LGA, >90th centile) rate of 8.8.

Table 1: Characteristics of the study population (n = 134,425).

	n	%	Mean	SD	Median	IQR
Maternal height, cm	–	–	166.6	5.9	167.0	7.0
Maternal weight, kg	–	–	64.7	12.3	62.0	14.0
Maternal age, years	–	–	30.0	4.7	29.5	7.0
<20	1508	1.1	–	–	–	–
20–30	67,273	50.1	–	–	–	–
30–35	46,334	34.5	–	–	–	–
35–40	16,558	12.3	–	–	–	–
≥40	2752	2.0	–	–	–	–
BMI, kg/m^2	–	–	23.3	4.2	22.3	4.6
<18.5	6923	5.2	–	–	–	–
18.5–25	93,764	69.8	–	–	–	–
25–29.9	23,498	17.5	–	–	–	–
≥30	10,240	7.6	–	–	–	–
Parity	–	–	–	–	–	–
0	66,478	49.5	–	–	–	–
1	49,922	32.6	–	–	–	–
2	13,758	15.3	–	–	–	–
≥3	4267	11.6	–	–	–	–
Smoking	–	–	–	–	–	–
0	120,679	89.8	–	–	–	–
1–9	9347	7.0	–	–	–	–
10–19	3743	2.8	–	–	–	
≥20	656	0.5	–	–	–	–
Pre-existing diabetes	349	0.3	–	–	–	–
Gestational diabetes	4413	3.3	–	–	–	–
Pre-existing hypertension	1163	0.9	–	–	–	–
Gestational hypertension	5080	3.8	–	–	–	–
Premature delivery (<37 weeks)	7283	5.4	–	–	–	–
Gestation at delivery, days	–	–	276.6	12.9	279.0	11.0
Birthweight, g	–	–	3389.5	535.8	3420.0	610.0
Sex	–	–	–	–	–	–
Male	69,154	51.4	–	–	–	–
Female	65,271	48.6	–	–	–	–
Stillbirth	613	4.2	/1000			

BMI, body mass index; IQR, interquartile range; SD, standard deviation.

Discussion

This is to our knowledge the first study to report coefficients for customised birthweight standard in a Slovenian population.

Comparison with datasets from other countries is facilitated by centring the multiple regression run on a standard mother, defined as a nullipara with height 163 cm and weight 64 kg and a gestation length of 280 days [19]. The constant or birthweight for such a “standard mother” was 3451 g (Table 2), which is remarkably similar to constants in a previous comparison of European origin mothers in England (3456 g), the US (3453 g), Australia (3464 g) and New Zealand (3464 g) [20]. The analysis has also demonstrated that the same physiological variables affect birthweight as observed previously [17–21] and include maternal height, weight, parity as well as the sex of the fetus. The magnitude of effect is comparable to previous analyses. For example, the coefficient for maternal height is 7.9 g, and ranged from 6.4 to 9.6 in four countries analysed [20]; similarly, the linear coefficient for maternal weight was 8.7, and ranged from 7.6 to 9.2 [20]. We could not assess ethnic variation as >99% of our population are Slovenian.

Pathological factors resulting from the multiple regression analysis also reflect previous findings [20]. For example, smoking again demonstrates a dose-dependent relationship with birthweight, rising from a deficit of 110 g (1–9 cigarettes a day) to 171 g (10–19) and 202 g (≥20). Similarly, obesity is strongly associated with a birthweight deficit which increases to −94 g for mothers with a BMI of ≥35.

The richness of our dataset allowed for the first time the derivation of coefficients for low and high maternal age. Often when this variable is entered into the analysis, it is not significant because of correlation with parity. Here, maternal age shows a mild but significant birthweight deficit with a U-shaped distribution. The highest effect is a still modest deficit of 28.4 g in mothers aged 40 and over, which is consistent with observations of increased risk of placental dysfunction in older mothers [21].

We were also, for the first time, able to differentiate between the effects of pre-existing and gestational diabetes, the former at +169 g having a more than five-fold increased effect on birthweight than gestational diabetes (30 g). The effect of pre-existing diabetes has varied in other studies – for example, it was higher in the US (+242 g) [20] and lower in Ireland (137 g) [22]. Such variation could reflect different patient populations, or differential successes with blood sugar control during pregnancy.

The inclusion of pathological variables in the analysis results in a constant which is therefore free from such pathological influences on birthweight. The actual effect on the magnitude of the constant derived in the multiple regression model depends on the prevalence of these pathological factors, which in this database is not high (see Table 1).

The coefficients allow adjustment of the term optimal weight according to the physiological/constitutional characteristics of the mother. To illustrate this effect, according to the coefficients listed in Table 2, a mother who is only slightly and symmetrically, i.e. with the same BMI – smaller

Table 2: Coefficients from the multiple regression model.

	Coefficient	SE	95% CI
Constant at 280 days	3451.3		
Gestational age (from 280 days)			
Linear	19.1	0.2	18.6 to 19.6
Quadratic	−0.48	0.02	−0.51 to −0.45
Cubic	−0.004	0.001	−0.006 to −0.001
Sex			
Male	78.4	2.1	74.3 to 82.5
Female	−78.4	2.1	−82.5 to −74.3
Maternal height (from 163 cm)			
Linear	7.9	0.3	7.3 to 8.5
Maternal weight (from 64 kg)			
Linear	8.7	0.2	8.3 to 9.2
Quadratic	−0.12	0.01	−0.14 to −0.1
Cubic	0.0007	0.0002	0.0004 to 0.0011
BMI, kg/m^2 (from 18.5 to 25)			
<18.5	−14.1	5.9	−25.7 to −2.6
25–30	−23.0	4.6	−32.1 to −14
30–35	−63.6	9.1	−81.3 to −45.8
≥35	−94.0	15.4	−124.3 to −63.8
Maternal age (from 20 to 30 years)			
30–35	−5.6	2.4	−10.4 to −0.9
35–40	−13.2	3.6	−20.2 to −6.2
≥40	−28.4	7.9	−43.9 to −13
Parity (from 0)			
1	108.3	2.4	103.6 to 113
2	140.5	3.8	133 to 148
≥3	159.0	6.4	146.4 to 171.6
Smoking (from 0)			
1–9	−109.9	4.2	−118.1 to −101.7
10–19	−170.9	6.5	−183.7 to −158.1
≥20	−202.3	15.6	−232.9 to −171.8
Diabetes – pre-existing	169.1	21.8	126.3 to 211.9
Diabetes – gestational	30.0	6.1	18.2 to 41.9
Hypertension – pre-existing	−55.7	12.1	−79.5 to −32
Hypertension – gestational	−79.7	5.9	−91.3 to −68.1

BMI, body mass index; CI, confidence interval; SE, standard error. n = 126,627; adjusted R^2: 0.263; standard error of regression: 375.9; coefficient of variation (CV): 0.1089.

than the "standard" mother, say 158 cm tall and weighing 57 kg, would be expected to have a baby weighing approximately 100 g less: [(163–158 cm = 5 × 7.9 g) = 39.5 g] plus [(64–57 kg) = 7 × 8.7 g = 60.9 g = total–100.4 g less. At the normal limits of the distribution, i.e. the 10th and 90th centile, such a 100 g variation will result in "SGA" being mis-diagnosed in 40% of cases [13].

Applying the derived coefficients to the original database has resulted in SGA and LGA rates (11.9 and 8.8%, respectively) that are similar to those observed in other populations [28]. SGA rates tend to be higher than 10% when applying a pathology-free, "optimal" standard because in any unselected population it is more likely that pregnancies are more affected by growth restricting factors (e.g. smoking, hypertensive diseases, placental insufficiency) than macrosomic factors (e.g. diabetes).

The strength of our study was an ethnically homogenous population with complete data for deriving customised birthweight standards. Variables were collected according to a standardised methodology and pre-made definitions. A potential weakness is incorrect data input through human or computer error. However, this risk is minimised in NPIS by controls that have been built in the computerised system and by quality checks performed by the Slovenian National Institute of Public Health.

For better performance, a birthweight standard should be fully and not just partially customised. Compared to a non-customised birthweight standard, a Scotland population-based study [23] has shown that partial customization due to lack of data on maternal weight and ethnicity does not improve prediction of adverse neonatal outcome including infant death, stillbirth, overall mortality (infant and stillbirth), Apgar score <7 at 5 min and admission to the neonatal unit.

Additional analyses in an independent UK cohort suggested that lack of data on ethnicity in this population (in which national statistics show 98% are white British) and maternal weight would have misclassified approximately 15% of the LGA fetuses [23]. A Cochrane review has found no randomised studies to compare customised vs population-based growth standards [24]. However, it has been argued that randomised controlled trials (RCTs) are not the appropriate tools to test standards; instead, they require large databases with hard outcomes [13].

In comparative studies of several birthweight databases, SGA based on customised growth potential is more strongly associated than SGA based on respective population standards with pregnancy complications and adverse outcomes, including abnormal antenatal Doppler, fetal distress, caesarean section, admission and length of stay in neonatal intensive care and stillbirths and neonatal deaths [4, 5, 8, 10, 25].

Customisation has also proved superior to the recently promoted INTERGROWTH-21st [26] international population-based standard in a multi-ethnic maternity population in Auckland [27], New Zealand. When the birthweight standard was customised for maternal height, weight, parity and ethnicity, it identified 11.6% of infants as SGA and at risk, with a two-fold increased risk of neonatal morbidity and mortality and a three-fold increased risk of stillbirth. In contrast, only 4.6% of cases were SGA by INTERGROWTH-21st, and most pregnancies at risks of adverse neonatal outcome and stillbirth were missed [27].

These results have recently been confirmed in a comparative study of a database of 1.2 million births from 10 countries. Customised standards specific to each country and ethnic group resulted in increased sensitivity in detecting SGA babies at risk of stillbirth. In contrast, SGA rates according to INTERGROWTH-21st failed to identify most adverse outcomes, and tended only to reflect maternal constitutional characteristics [28].

Availability of a Slovenian set of coefficients for an adjustable standard will allow improved calculation of birthweight centiles and the computer-assisted prediction of the “term optimal weight” for each pregnancy. This in turn is combined with a fetal weight proportionality formula [18] to produce customised antenatal growth curves for surveillance of fetal weight gain [29].

In conclusion, development of customised birthweight standards for a Slovenian population will aid clinicians in Slovenia to improve the distinction between normal and abnormal SGA fetuses [8], thus avoiding unnecessary preterm delivery and improving long-term outcomes in children, and in better understanding of the impact of physiological and pathological factors on fetal growth.

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