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OBSTETRICS

The Danish newborn standard and the International Fetal and Newborn Growth Consortium for the 21st Century newborn standard: a nationwide register-based cohort study

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BACKGROUND: It is a matter of debate whether 1 universal standard, such as the International Fetal and Newborn Growth Consortium for the 21st Century standard, can be applied to all populations.

OBJECTIVE: The primary objective was to establish a Danish newborn standard based on the criteria of the International Fetal and Newborn Growth Consortium for the 21st Century standard to compare the percentiles of these 2 standards. A secondary objective was to compare the prevalence and risk of fetal and neonatal deaths related to small for gestational age defined by the 2 standards when used in the Danish reference population.

STUDY DESIGN: This was a register-based nationwide cohort study. The Danish reference population included 375,318 singletons born at 33 to 42 weeks of gestation in Denmark between January 1, 2008, and December 31, 2015. The Danish standard cohort included 37,811 newborns who fulfilled the criteria of the International Fetal and Newborn Growth Consortium for the 21st Century standard. Birthweight percentiles were estimated using smoothed quantiles for each gestational week. The outcomes included birthweight percentiles, small for gestational age (defined as a birthweight of 3rd percentile), and adverse outcomes (defined as either fetal or neonatal death).

RESULTS: At all gestational ages, the Danish standard median birthweights at term were higher than the International Fetal and Newborn Growth Consortium for the 21st Century standard median birthweights: 295g for females and 320 g for males. Therefore, the estimates of the prevalence rate of small for gestational age within the entire population were different: 3.9% (n=14,698) using the Danish standard vs 0.7% (n=2640) using the International Fetal and Newborn Growth Consortium for the 21st Century standard. Accordingly, the relative risk of fetal and neonatal deaths among small-for-gestational-age fetuses differed by SGA status defined by the different standards (4.4 [Danish standard] vs 9.6 [International Fetal and Newborn Growth Consortium for the 21st Century standard]).

CONCLUSION: Our finding did not support the hypothesis that 1 universal standard birthweight curve can be applied to all populations.

Key words: birthweight, fetal death, fetal growth restriction, International Fetal and Newborn Growth Consortium for the 21st Century, neonatal death, obstetrical ultrasound, register, small for gestational age, standard

Introduction

Controversies exist on the possibility to establish normal birthweight (BW) standards for each gestational age (GA) that apply to all populations worldwide. Normal BW standard is of interest for both clinicians and epidemiologists, as small-for-gestational-age (SGA) fetuses are at increased risk of adverse outcomes, including fetal death[1,2] and long-term consequences after childbirth.[3–6] In obstetrical practice, the performance to identify SGA fetuses depends on the definition of SGA (such as a BW of 10th or 2.5th percentile[7]), the growth curve being used (reference curves or standard curves), and the predictive ability of the fetal weight estimation by ultrasound examination, which, in a Danish context, might not be improved by an estimate based on longitudinal scans compared with a single scan.[8]

It is a challenge that "reference curves," which are based on an entire population and thereby include both risk factors for disease and people with diseases, differ markedly between populations.[9–12] These differences between the curves have been attributed to differences among populations concerning ethnicity, state of nutrition, rate of obstetrical complications, access to health services, and prevalence of maternal medical complications. Therefore, some have argued in favor of "standard curves," which are based on a subgroup of a population and only include pregnancies supposed to be normal as they fulfill strict inclusion criteria.[13] It is hypothesized that fetuses have identical growth potential in all populations, which is why the "standard curves" should be identical in all populations.[14–16] Thus, a "standard curve" describes how fetuses should grow, as opposed to "reference curves," which describe how fetuses have grown.

In 2014, the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) published an international standard BW curve based on a multicenter and multiethnic population that should allow comparison across populations. According to their hypothesis, this INTERGROWTH-21st standard BW curve is universal.[15] Here, we aimed to

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AJOG at a Glance

Why was this study conducted?

Standard birthweight (BW) curves define normal BW. However, it is a matter of debate whether 1 universal standard, such as the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) standard, can be applied to all populations.

Key findings

The Danish standard median BW at term was 300 g higher than the INTERGROWTH-21st standard median BW. The prevalence rates of small-for-gestational-age (SGA) fetuses within the entire population were 3.9% (n=14,698) using the Danish standard and 0.7% (n=2640) using the INTERGROWTH-21st standard. The relative risk of adverse outcomes among SGA fetuses differed by SGA status defined by the different standards (4.4 [Danish standard] vs 8.8 [INTERGROWTH-21st standard]).

What does this add to what is known?

Compared with the Danish standard, the universal INTERGROWTH-21st standard led to lower BW medians and fewer SGA neonates with higher risks of fetal and neonatal deaths. Our findings did not support the hypothesis that 1 universal standard BW curve can be applied to all populations.

evaluate this INTERGROWTH-21st hypothesis. Therefore, we compared the INTERGROWTH-21st standard BW curve with the Danish standard BW curve based on the criteria from the INTERGROWTH-21st.[13] A secondary aim was to evaluate the difference in fetal and neonatal deaths related to SGA status when using the 2 standard BW curves.

Materials and Methods

Data sources

All Danish residents are assigned a unique civil registration number at the time of birth or immigration, enabling linkage of all Danish registries on the individual level. Information on migrations and vital status are continuously updated, allowing follow-up studies on a whole population.[17] The Danish healthcare system is tax funded, and all residents have equal access to healthcare services. Data on pregnancies were retrieved from the Danish Fetal Medicine Database,[18] which combines information from each Department of Obstetrics in Denmark (Astraia Software GmbH; version 1.24.10). Maternal and neonatal delivery data were retrieved from the Danish Medical Birth Registry.[19] The Danish National Patient Registry[17] holds data on the diagnosis and treatment at ambulant visits and hospitalizations. Moreover, the registry was used in combination with the Danish National Prescription Registry,[20] where all prescription-based medicine claimed at Danish pharmacies are registered, to retrieve information on maternal medical history and previous obstetrical history.

Study design and population

This study was a nationwide cohort study based on prospectively collected data from Danish administrative registries. We included all pregnancies with the date of birth from January 1, 2008, to December 31, 2015, in Denmark. The due date was determined on the basis of ultrasound, as this is standard in Denmark, either at the first-trimester nuchal translucency ultrasound (>94%) using crown-rump length measures[21] or at second-trimester malformation scan (<6%) using biparietal diameter.[18,22,23]

We defined 2 populations: the Danish reference population, which included the entire population, including patients with pregnancies at risk, and a Danish standard cohort, which was derived from the Danish reference population, but only consisted of patients with low-risk pregnancies according to the INTERGROWTH-21st criteria.

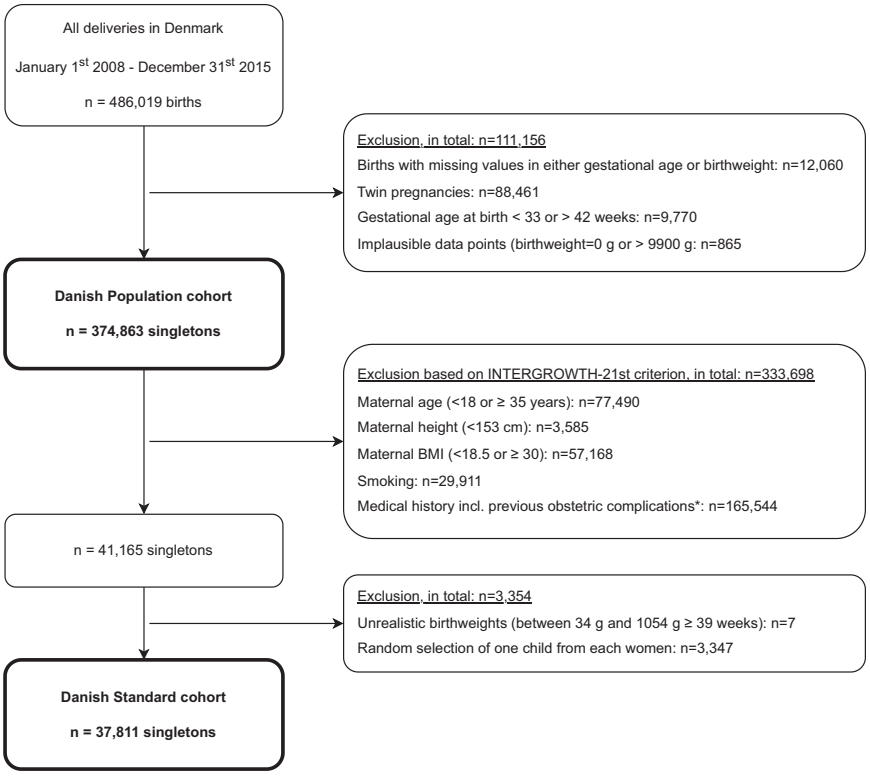
The Danish reference population

The study population, the Danish reference population, included all singleton pregnancies with the date of birth from January 1, 2008, to December 31, 2015, in Denmark. The exclusion criteria were missing data of either BW or GA at birth or GA at birth <33 or > 42 weeks of gestation (Figure 1). Moreover, 865 implausible data points were excluded from further analysis (Figure 1).

The Danish standard cohort

The Danish standard cohort was retrieved from the Danish reference population (Figure 1). To extract only healthy women with uncomplicated pregnancies, we used INTERGROWTH-21st exclusion criteria: age <18 and ≥35 years, maternal body mass index <18.5 and ≥30 kg/m^2, maternal height <153 cm, previous complicated pregnancies (preeclampsia or eclampsia or hemolysis, elevated liver enzymes, and low platelet count; preterm delivery [<37 0/7 weeks of gestation]; BW <2500 g or >4500 g; neonatal or fetal death; congenital malformations; or miscarriage in more than 1 of 2 previous consecutive pregnancies), smoking during pregnancy, use of alcohol during pregnancy with consequences for the infant, proteinuria, blood pressure of ≥140 mm Hg (systolic) and/or ≥90 mm Hg (diastolic) any time during pregnancy, fetal anomaly or congenital disease in the current pregnancy, anemia, sexually transmitted disease during pregnancy, pregnancies after fertility treatment, and relevant past medical history with the need for long-term medication. The specific International Classification of Diseases, Tenth Revision (ICD-10, codes and the Anatomical Therapeutic Chemical Classification System (ATC) codes used for this selection of the Danish standard cohort are listed in Supplemental Tables 1 and 2. ICD-10 codes are available for all outpatient visits and admissions in

FIGURE 1
Flowchart of the study population



Asterisk denote medical history, including previous obstetrical complications, is defined following the INTERGROWTH-21 Project criteria, which is relevant diagnosis or ATC codes 6 months before or during pregnancy (9 months) (a total of 15 months before delivery). A full list of the used diagnosis and ATC codes are provided in Supplemental Tables 1-2.

ATC, Anatomical Therapeutic Chemical Classification System; *BMI*, body mass index; *INTERGROWTH-21st*, International Fetal and Newborn Growth Consortium for the 21st Century.

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Denmark. ATC codes are available for all prescription medicine handed out at pharmacies in Denmark. ICD-10 codes and ATC codes were classified as relevant past medical history if the out-patient visit, hospital admission, or drug dispensing dates were within 15 months before birth.

According to INTERGROWTH-21st,[13] the pregnant women must not be employed in situations where there is a risk of exposure to chemicals or toxic substances or very physically demanding activity, including contact or vigorous sports and scuba diving or similar activities. Information regarding occupational risk is not available in the aforementioned registries and databases, but any risk for the pregnant women is addressed at the first pregnancy examination by the general practitioner. If there is any occupational risk, sick leave will be recommended. Therefore, this exposure during pregnancy is considered not to be relevant in Denmark. Moreover, the women in INTERGROWTH-21st should not have evidence of socioeconomic constraints likely to impede fetal growth identified using local definitions of social risk. In Denmark, the social system ensures unemployment benefits and reduces this problem to a minimum.

Moreover, 7 unrealistic BWs for term deliveries were excluded from further analysis (Figure 1). After applying the INTERGROWTH-21st exclusion criteria, we randomly selected 1 pregnancy from each woman to avoid dependent data (Figure 1).

Outcomes

BW, neonatal sex, and GA at birth were used to calculate BW percentiles for both the Danish standard cohort and the Danish reference population.

Adverse outcomes were fetal death (defined as death before delivery) and neonatal death (defined as death within 28 days after delivery).

Statistical analyses

We employed quantile regression to obtain the BW curves without parametric distribution assumptions.[24] In detail, for both the Danish reference population and the Danish standard cohort, nonparametric quantile regressions within a locally polynomial framework modeled the relation between GA and BW. The quantile regressions are fitted as univariate models, increasing the comparability to the INTERGROWTH-21st standard curves. Partially linear fitting between adjacent gestational weeks and piecewise cubic polynomials with 3 to 5 knots permit feasible smooth curves.[25] This method is robust for the 3% and 97% quantiles, especially in the registry data. The INTERGROWTH-21st standard BW curve is restricted to 33 weeks of gestation as the lower limit. Therefore, 33 weeks of gestation is also the lower limit in both the Danish standard BW curve and the Danish reference population BW curve. We fitted separate models for boys and girls. The models were fitted with SAS (version 9.4; SAS Institute Inc, Cary, NC; updated to version 13.2) and R (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria).

Ethical approval

Data handling was approved by the Danish Data Protection Agency (2008-58-0028), through a regional notification (internal reference: 2017-67). All data handling was performed within the environment of Statistics Denmark in an anonymous setup, where individuals cannot be identified, but enabling linkage between different registries and databases on the individual level.[26] Retrospective register-based studies do not require ethical approval in Denmark.

TABLE 1
Maternal and neonatal characteristics

Characteristics	INTERGROWTH-21st standard (n=20,486)	Danish standard (n=37,811)	Danish reference population (n=375,318)
Maternal age (y)	28.0±4.0	29.3±3.3	30.4±4.9
Maternal height (cm)	161.8±5.6	168.1±6.2	167.9±6.5
Maternal weight (kg)	61.3±8.6	64.4±9.2	69.0±15.4
Maternal BMI (kg/m^2)	23.4±2.9	22.2±2.5	24.5±7.8
Ethnicity			
African Caribbean	—	326 (0.9)	3599 (1.0)
Asian	—	934 (2.5)	8194 (2.2)
White	—	35,127 (92.9)	349,484 (93.1)
Oriental	—	579 (1.5)	4741 (1.3)
None of the above	—	646 (1.7)	6557 (1.7)
Missing	—	199 (0.5)	2743 (0.7)
Nonsmoking	—	37,811 (100.0)	326,164 (86.9)
Nulliparous	12,996 (63.4)	18,199 (48.5)	171,022 (45.6)
Spontaneous initiation of labor	13,470 (65.8)	33,308 (88.1)	294,130 (78.4)
Cesarean delivery	7452 (36.4)	5409 (14.3)	76,349 (20.3)
NICU admission longer than 1 d	1184 (5.8)	966 (2.6)	18,237 (4.9)
Preterm birth (<37 wk)	1136 (5.5)	552 (1.5)	15,096 (4.0)
Term low BW (≥37 wk and <2500 g)	651 (3.2)	204 (0.5)	4138 (1.1)
All low BW (<2500 g)	1129 (5.5)	365 (1.0)	9954 (2.7)
Neonatal mortality (<28 d)	22 (0.10)	19 (0.10)	210 (0.06)
Boys	10,482 (51.2)	19,326 (51.1)	197,477 (51.3)
Term BW at ≥37 wk (g)	3300±500 g	3597±465 g	3521±513 g
Weight measures	BWs	BWs	BWs

Data are presented as mean±standard deviation for continuous variables and number (percentage) for categorical variables.

BMI, body mass index; *BW*, birthweight; *INTERGROWTH-21st*, International Fetal and Newborn Growth Consortium for the 21st Century; *NICU*, neonatal intensive care unit.

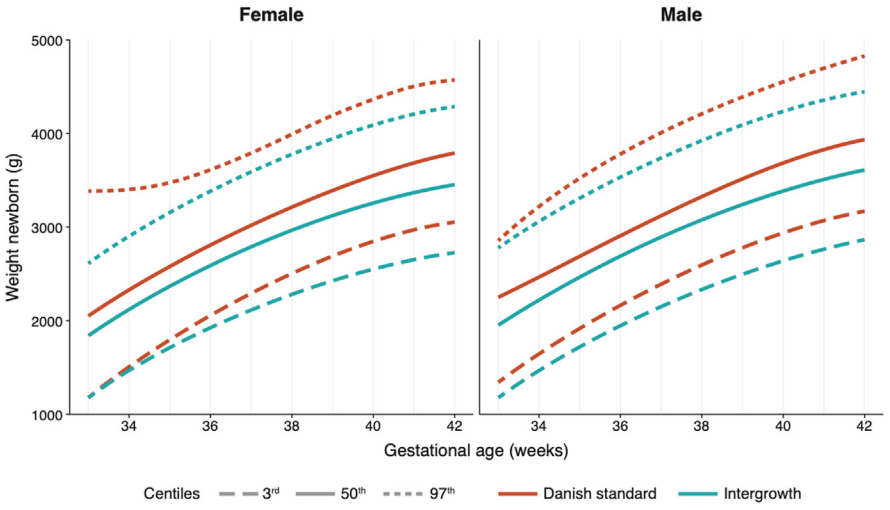
Hansen. The Danish newborn standard and the International Fetal and Newborn Growth Consortium for the 21st Century newborn standard. Am J Obstet Gynecol 2023.

Results

The Danish reference population included 375,318 singleton unselected pregnancies among which 37,811 newborns from the Danish standard cohort fulfilled the INTERGROWTH-21st criteria (Figure 1). Compared with the INTERGROWTH-21st standard cohort, the Danish standard cohort had higher median maternal height (INTERGROWTH-21st standard cohort: 161.8±5.6 [95% confidence interval, 161.7−161.9]; Danish standard cohort: 168.1±6.2 [95% CI, 168.0−168.2]), maternal weight (INTERGROWTH-21st standard cohort: 61.3±8.6 [95% CI, 61.2−61.4]; Danish standard cohort: 64.4±9.2 [95% CI, 64.3−64.5]), age (INTERGROWTH-21st standard cohort: 28±4 [95% CI, 28.0−28.1]; Danish standard cohort: 29.3±3.3 [95% CI, 29.3−29.3]), and parity (nulliparous; INTERGROWTH-21st standard cohort: 63.4% [95% CI, 63.0-64.0]; Danish standard cohort: 48.5% [95% CI, 48.0−49.0]) (Table 1).

At all GAs, the BW medians (BW of 50th percentile) defined by the Danish standard were higher than those defined by the INTERGROWTH-21st standard. Thus, at term (40 0/7 weeks of gestation), compared with the INTERGROWTH-21st standard median BW, the Danish standard median BW was 320 g higher in boys (3380 vs 3700 g) and 295 g higher in girls (3260 vs 3555 g) (Figure 2; Supplemental Tables 4 and 5). The BW medians (BW of 50th percentile) of the full Danish reference population were very similar to those of the Danish standard cohort; at term, the difference was 20 g (3680 g vs 3700 g) in boys and 19 g (3536 g vs 3555 g) in girls (Supplemental Tables 3 and 5). The prevalence of SGA in the Danish reference population differed substantially depending on whether the definition was based on a BW of 3rd percentile in the INTERGROWTH-21st standard cohort (0.7%; n=2640) or a BW of 3rd percentile in the Danish

FIGURE 2
Birthweight curves for the INTERGROWTH-21st and Danish standard cohorts



Each cohort is marked with different lines: the Danish standard cohort (*red line*) and the INTERGROWTH-21st Project standard cohort[15] (*blue line*). For each cohort, the percentiles are marked with different lines: 3rd percentile (*dashed line*), 50th percentile (*solid line*), and 97th percentile (*dotted line*).

INTERGROWTH-21st, International Fetal and Newborn Growth Consortium for the 21st Century.

Hansen. The Danish newborn standard and the International Fetal and Newborn Growth Consortium for the 21st Century newborn standard. Am J Obstet Gynecol 2023.

standard cohort (3.9%; n=14,698) (Table 2).

The fetal death rate (Table 2) was 1.2 in every 1000 pregnancies in the Danish reference population, whereas it was 4.8 among the 14,698 SGA (BW of <3rd percentile) fetuses defined by the Danish standard cohort and 10.6 among the 2640 SGA fetuses defined by the INTERGROWTH-21st standard cohort. Among non-SGA pregnancies, these figures were 1.1 (Danish standard cohort) and 1.1 (INTERGROWTH-21st standard cohort) equivalent to relative risks (RRs) of 4.4 (Danish standard cohort) and 9.6 (INTERGROWTH-21st standard cohort) (Table 2).

The neonatal death rate (Table 2) was 0.6 in every 1000 pregnancies in the Danish reference population, whereas it was 1.9 among SGA (BW of 3rd percentile) fetuses defined by the Danish standard cohort and 5.3 among SGA fetuses defined by the INTERGROWTH-21st standard cohort. Among non-SGA pregnancies, these figures were 0.5 (Danish standard cohort) and 0.5 (INTERGROWTH-21st standard cohort) equivalent to RRs of 3.8 (Danish standard cohort) and 10.6 (INTERGROWTH-21st standard cohort) (Table 2).

For comparison, equivalent results regarding fetal and neonatal death rates using a BW of 10th percentile as the SGA definition are provided in Supplemental Figure 1 and Tables 5-7.

Comment

Principal findings

Here, we demonstrated that the BW percentiles defined by the Danish standard, including uncomplicated pregnancies from healthy women selected following the INTERGROWTH-21st criteria, were markedly higher than those defined by the universal INTERGROWTH-21st standard. Accordingly, the number of neonates classified as SGA (BW of <3rd percentile) increased from 0.7% with the use of the INTERGROWTH-21st standard to 3.9% when defined by the Danish standard. The RRs of fetal and neonatal deaths were at least doubled among SGA defined by the INTERGROWTH-21st standard compared with SGA defined by the Danish standard. However, most fetal and neonatal deaths occurred in non-SGA fetuses, when defined either by

TABLE 2
Fetal and neonatal deaths in the Danish reference population according to SGA definition (BW of 3rd percentile) by INTERGROWTH-21st and Danish standards

		INTERGROWTH-21st standard		Danish standard	
	Total Danish reference population (N=375,318)	SGA (BW<3rd percentile) (n=2640)	Non-SGA (n=372,678)	SGA (BW<3rd percentile) (n=14,698)	Non-SGA (n=360,620)
Outcome	Number (per 1000 pregnancies)	Number (per 1000 pregnancies)	Number (per 1000 pregnancies)	Number (per 1000 pregnancies)	Number (per 1000 pregnancies)
Fetal death	455 (1.2)	28 (10.6)	427 (1.1)	71 (4.8)	384 (1.1)
Neonatal death at <28 d	210 (0.6)	14 (5.3)	196 (0.5)	28 (1.9)	182 (0.5)

BW, birthweight; *INTERGROWTH-21st*, International Fetal and Newborn Growth Consortium for the 21st Century; *SGA*, small for gestational age.

Hansen. The Danish newborn standard and the International Fetal and Newborn Growth Consortium for the 21st Century newborn standard. Am J Obstet Gynecol 2023.

INTERGROWTH-21st or Danish standards.

Results in the context of what is known

The variation in BW between populations is well known, but it remains a matter of debate whether 1 universal standard BW curve can be applied to all populations. According to the INTERGROWTH-21st standard, 1 universal standard[15,27] can be applied worldwide. However, the National Institute of Child Health and Human Development suggests ethnic-specific standard curves.[28] Furthermore, the World Health Organization (WHO) has published a multinational standard but recommends that the standard be used with caution and local adjustments.[29,30]

Our findings add to this discussion. Thus, a BW of 50th percentile at term is approximately 300 g higher in the Danish standard cohort than in the INTERGROWTH-21st standard cohort, although approximately 50 g (7.6 g/cm[31]) of this difference can be explained by a 6-cm difference in maternal height (Supplemental Table 3). The rest of the difference must rely on other factors, including ethnic differences and differences in socio-economic status.

Previous studies on this topic share the same finding that the BW percentiles from the INTERGROWTH-21st standard curve are lower than the BW percentiles based on local curves. However, none of these studies adhered strictly to the INTERGROWTH-21st criteria but used local criteria,[16,30] local population reference,[32–35] or customized growth charts,[36,37] which may explain why the difference of 300 g at term as demonstrated in our study remains larger than the difference presented in previous studies.

The interpretation of the data from different studies is challenging. The authors of the INTERGROWTH-21st Project[15] argue in favor of 1 universal INTERGROWTH-21st standard BW curve,[15,27] as the difference in median BW between India (2.9 kg) and the United Kingdom (3.5 kg) can be attributed only to 1.9% to 3.5% population difference. Contrary to this, the WHO considers it prudent to test the universal standard curve in each population to see if adjustments are required to meet local needs.[30] They argue that differences remain between ethnic groups with equal healthcare conditions and maternal characteristics.[29,30] In addition, our study supports the idea of local BW standards.

Clinical implications

The Danish standard curve is almost identical to the unselected Danish reference population curve. Our finding supported the validity of the Danish standard BW curve, as one would expect that normal BW defined by a standard curve would be higher than normal BW defined by a population reference curve—as the reference curve includes pathologic pregnancies associated with SGA.[38] The 2 curves being almost identical demonstrates that the proportion of pathology in the Danish reference population is rather low.

For both standards, SGA was associated with an increased risk of fetal and neonatal deaths compared with non-SGA. The risk of fetal and neonatal deaths associated with SGA was doubled using the INTERGROWTH-21st standard compared with SGA defined by the Danish standard. However, when using the I INTERGROWTH-21st standard, the total number of SGA fetuses was reduced, and a larger proportion of fetal and neonatal deaths occurred in non-SGA pregnancies. Thus, SGA is not the only risk factor for adverse pregnancy outcomes. To improve the classification of high-risk pregnancies, additional markers reflecting placental function need to be considered. In current obstetrical practice, these markers may include Doppler ultrasound estimates of maternal, fetal, and umbilical blood flows and placental serum markers.[39–44] Moreover, here, we used a BW of 3rd percentile to define SGA. We used this definition as we aimed to identify those fetuses truly at risk of placental dysfunction based on fetal size alone. This definition is in line with previous publications[45]; however, other definitions may be used in clinical practice. In some countries, a BW of 10th percentile is used to define SGA.[46] Using this definition, the sensitivity of fetuses at risk increases, but the positive predictive value will be low (Tables S6 and S7). Thus, in a clinical setting, the performance of detecting fetuses at risk may vary according to the growth curve and SGA definition being used.

Research implications

This study was based on data from the Danish registries. However, a prospective study is necessary before implication. A prospective study would allow for the inclusion of additional markers of placental dysfunction. Moreover, in future research, additional markers reflecting placental function should be considered to identify those fetuses truly at risk of placental dysfunction rather than defining SGA based on fetal size alone.

Strengths and limitations

The strengths of this study are the validity of the registries,[17–20] the size of the standard cohort, the strict adherence to the INTERGROWTH-21st criteria, and the use of the INTERGROWTH-21st statistical methods. A limitation of this study is the register-based design, as we cannot exclude some misclassification despite the high validity of the Danish registries. However, as the misclassification may include some diseases in the Danish standard, the differences may be underestimated. The number of births at GA of 32 weeks was low, and the Danish standard BW of 97th percentile estimation seemed unrealistic, as this percentile has a different course compared with the other percentiles. Moreover, the Danish standard BW of 97th percentile in females was higher at 33 and 34 weeks of gestation than the equivalent curve in males (Figure 2; Table 2).

Conclusion

When comparing the INTERGROWTH-21st standard with the Danish standard, BW medians were lower, the prevalence of SGA was reduced, and the risk associated with SGA was higher. These

findings did not support the hypothesis that 1 universal standard BW curve can be applied to all populations. ■

GLOSSARY

BW, birthweight
CI, confidence interval
GA, gestational age
INTERGROWTH-21st, International Fetal and Newborn Growth Consortium for the 21st Century
RR, relative risk
SD, standard deviation
SGA, small for gestational age

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