

RESEARCH ARTICLE

Evaluation of the INTERGROWTH-21st project newborn standard for use in Canada

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Abstract

Objective

To evaluate the performance of the INTERGROWTH-21st Project newborn standard vis-a-vis the current Canadian birth weight-for-gestational age reference.

Methods

All hospital-based singleton live births in Canada (excluding Quebec) between 2002 and 2012 with a gestational age between 33 and 42 weeks were included using information obtained from the Canadian Institute for Health Information. Small- and large-for gestational age centile categories of the INTERGROWTH standard and Canadian reference were contrasted in terms of frequency distributions and rates of composite neonatal morbidity/mortality.

Results

Among 2,753,817 singleton live births, 0.87% and 9.63% were <3rd centile and >97th centile, respectively, of the INTERGROWTH standard, while 2.27% and 3.55% were <3rd centile and >97th centile, respectively, of the Canadian reference. Infants <3rd centile and >97th centile had a composite neonatal morbidity/mortality rate of 46.4 and 12.9 per 1,000 live births, respectively, under the INTERGROWTH standard and 30.9 and 16.6 per 1,000 live births, respectively, under the Canadian reference. The INTERGROWTH standard <3rd centile and >97th centile categories had detection rates of 3.14% and 9.74%, respectively, for composite neonatal morbidity/ mortality compared with 5.48% and 4.60%, respectively for the Canadian reference. Similar patterns were evident in high- and low-risk subpopulations.

study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Conclusions

The centile distribution of the INTERGROWTH newborn standard is left shifted compared with the Canadian reference, and this shift alters the frequencies and neonatal morbidity/mortality rates associated with specific centile categories. Further outcome-based research is required for defining abnormal growth categories before the INTERGROWTH newborn standard can be used.

Introduction

The INTERGROWTH-21st Project recently published international standards for fetal growth and newborn size created using a rigorous methodology [1,2]. These fetal growth and newborn size standards complement the World Health Organization's Child Growth Standards [3] and permit growth monitoring from early gestation through childhood. A key aspect of the INTERGROWTH-21st Project was the selection of a healthy cohort of fetuses from normal pregnancies in order to ensure that the resultant standard provides normative and prescriptive centiles of fetal and newborn growth. INTERGROWTH-21st project investigators suggest that their fetal and newborn growth standards will serve as worldwide standards for fetuses and newborns [1,2,4].

The INTERGROWTH-21st Project newborn birth weight-for-gestational age standard is based on the results of the multicentre, multiethnic, Newborn Cross-Sectional Study in which 20,486 eligible pregnant women were recruited from 8 sites worldwide [1]. Inclusion criteria ensured a healthy study population including (among others) site parameters related to altitude and pollution, and individual level factors such as maternal age, height, body mass index, smoking status, and medical and obstetric history. All women had ultrasound confirmed gestational age, and anthropometric measurements on the infants were completed within 12 hours after birth. The measurement devices used for anthropometry were calibrated twice weekly, and all measurements were standardized. Smoothed centiles of birth weight, length and head circumference were estimated at each gestational week between 33 and 42 weeks gestation using robust statistical techniques [2].

The rigorous design and analysis methods of the INTERGROWTH-21st Project notwithstanding, the clinical and public health consequences of switching from currently used fetal growth and newborn references to the INTERGROWTH-21st standards are unclear. We carried out an evaluation of the performance of the INTERGROWTH-21st Project birth weight-for-gestational age standard vis-a-vis the current Canadian birth weight-for-gestational age reference [5] by contrasting the frequency of centile categories for identifying growth abnormalities (including both small- and large-for-gestational age live births), and the rates of severe neonatal morbidity and neonatal mortality within these centile categories.

Methods

We carried out a retrospective cohort study of all singleton live births in Canada (excluding Quebec) for the period April 2002 to March 2013 (fiscal years 2002 to 2012) using information obtained from the Discharge Abstract Database of the Canadian Institute for Health Information. This database contains records of all hospitalizations in Canada (excluding Quebec) and includes approximately 98% of all births [6]. The collated data were abstracted from medical charts by trained medical records personnel using standardized definitions and included information on gestational age (obstetric estimate), birth weight, and maternal and newborn

diagnoses and interventions during the childbirth admission. During the study period all diagnoses were coded using the International Classification of Diseases 10th revision, Canadian modification (ICD-10 CA), while procedures were coded using the Canadian Classification of Health Interventions (CCI). Information in the database is routinely checked for accuracy, and validation studies have shown the information to be complete and accurate [7].

Live births between 33 and 42 weeks gestation were categorized into the conventional birth weight-for-gestational age centile categories for identifying small-for-gestational age live births, appropriate-for-gestational live births and large-for-gestational age live births using both the INTERGROWTH newborn standard [1] and the Canadian reference [5] (hereafter referred to as the INTERGROWTH and Canadian criteria). Centile categories of interest included birth weight for gestational age <3rd centile, 3rd to <10th centile, 10 to <50th centile, 50th to 90th centile, >90th to 97th centile and >97th centile. Frequency distributions of live births in the early and later years of the study period (2002–03 and 2011–12) and over the entire study period (2002–2012), were compared using centile categories based on both the INTERGROWTH and Canadian criteria. The frequency distribution of live births in specific low- and high-risk subpopulations were also compared within the respective centile categories. The high-risk categories of interest included infants affected by maternal hypertensive disorders (P00.0), infants of mothers with gestational diabetes (P70.0), and infants of diabetic mothers (P70.1). The low-risk categories included all live births and live births not affected by slow growth/malnutrition (P05), maternal hypertension (P00.0) or diabetes (P70.0).

Rates of severe neonatal morbidity (i.e., neonatal seizures (P90), assisted ventilation (1GZ31CAND, and 1GZ31CRND), assisted ventilation including continuous positive airway pressure (1GZ31CBND) and birth asphyxia (P20.1, P20.9 and P21)), and neonatal mortality were calculated among live births in the different centile categories based on the INTERGROWTH [1] and Canadian criteria [5]. Rates of composite neonatal morbidity (seizures, assisted ventilation, continuous positive airway pressure or birth asphyxia) and neonatal mortality were also estimated. The prognostic performance of the INTERGROWTH and Canadian criteria were also assessed in terms of the ability of the small- and large-for-gestational age centile categories to identify composite severe neonatal morbidity/mortality using rate ratios with 95% confidence intervals (CI) and detection (sensitivity) rates [8].

The study was carried out by the Canadian Perinatal Surveillance System of the Public Health Agency of Canada under its health surveillance mandate using publicly accessible anonymized data. Statistical analyses were carried out using SAS version 9 (Cary, NC).

Results

The study included 2,753,817 singleton live births. Overall between 2002 and 2012, the birth weight-for-gestational age of 0.87% of infants was <3rd centile of the INTERGROWTH criteria, compared with 2.27% of infants who were <3rd centile under the Canadian criteria ($P < 0.001$, Table 1). Similarly, a substantially lower proportion of live births were <10th centile of birth weight-for-gestational age of the INTERGROWTH criteria compared with the Canadian criteria. In contrast, a substantially larger proportion of live births were >97th and >90 centile under the INTERGROWTH criteria compared with the Canadian criteria (9.63% and 3.55% were >97th, respectively, $P < 0.001$). The patterns were evident both in 2002–03 and 2011–12 (Table 1).

Among infants affected by maternal hypertensive disorders, the proportion of live births <3rd centile was 5.65% under the INTERGROWTH criteria, while the same proportions were 9.31% under the Canadian criteria. Of the infants of mothers with gestational diabetes 1.31% were classified as <3rd centile by the INTERGROWTH criteria, while 2.77% were similarly

Table 1. Numbers and proportions of live births in birth weight-for-gestational centile categories of the INTERGROWTH -21st Project standard and the Canadian reference, Canada, 2002–12.

Period/ Standard or reference	Live Births	<3 rd centile		3 rd -<10 th centile		10 th -<50 th centile		50 th -90 th centile		>90 th -97 th centile		>97 th centile	
		No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
		All live births 2002–12											
INTERGROWTH std.	2,753,817	23,885	0.87	71,237	2.59	673,319	24.5	1,329,699	48.3	390,471	14.2	265,206	9.63
Canadian ref.	2,753,815	62,558	2.27	171,810	6.24	1,067,272	38.8	1,142,574	41.5	211,734	7.69	97,867	3.55
All live births 2002–03													
INTERGROWTH std.	398,327	3,688	0.82	10,399	2.32	95,176	21.3	190,713	42.6	57,823	12.9	40,528	9.05
Canadian ref.	398,327	9,496	2.12	24,412	5.45	151,233	33.8	166,108	37.1	31,999	7.15	15,079	3.37
All live births 2011–12													
INTERGROWTH std.	546,897	4,527	0.83	14,776	2.70	137,918	25.2	265,188	48.5	74,981	13.7	49,507	9.05
Canadian ref.	546,897	12,582	2.30	35,555	6.50	216,866	39.7	223,769	40.9	40,071	7.33	18,054	3.30
Infants affected by maternal hypertensive disorders 2002–12													
INTERGROWTH std.	6,217	351	5.65	568	9.14	1,919	30.9	2,188	35.2	638	10.3	553	8.89
Canadian ref.	6,217	579	9.31	867	14.0	2,245	36.1	1,879	30.2	370	5.95	277	4.46
Infants of mothers with gestational diabetes 2002–12													
INTERGROWTH std.	24,788	324	1.31	715	2.88	4,769	19.2	9,147	36.9	3,473	14.0	6,360	25.7
Canadian ref.	24,788	686	2.77	1,434	5.79	7,034	28.4	8,640	34.9	2,945	11.9	4,049	16.3
Infants of mothers with pre-existing diabetes 2002–12													
INTERGROWTH std.	10,521	99	0.94	199	1.89	1,266	12.0	2,945	28.0	1,605	15.3	4,407	41.9
Canadian ref.	10,521	178	1.69	409	3.89	1,922	18.3	3,230	30.7	1,668	15.9	3,114	29.6
Infants without slow growth/malnutrition or maternal hypertension/diabetes 2002–12													
INTERGROWTH std.	2,659,785	10,627	0.39	51,312	1.86	644,779	23.4	1,314,372	47.7	384,735	14.0	253,960	9.22
Canadian ref.	2,659,785	38,554	1.40	147,720	5.36	1,047,779	38.8	1,128,473	41.5	206,751	7.51	90,506	3.29

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classified by the Canadian criteria. On the other hand, 25.7% of the infants of mothers with gestational diabetes were >97th centile under the INTERGROWTH criteria, while 16.3% were classified as >97th under Canadian criteria. Infants of mothers with pre-existing diabetes showed similar patterns (Table 1) and essentially similar patterns were observed in the 3rd to <10th centile and the >90th to 97th centile categories.

Table 2 shows rates of severe neonatal morbidity and neonatal death among live births within specific centile categories of the INTERGROWTH and Canadian criteria. The rate of neonatal death was two-fold higher among live births <3rd centile of the INTERGROWTH criteria compared with the same rate among live births <3rd centile of the Canadian criteria (9.46 vs 4.67 per 1,000 live births, P <0.001, Fig 1). The rate of neonatal death was also higher among live births between the 3rd centile and <10th centile of the INTERGROWTH criteria compared with the Canadian criteria (P <0.001) and among live births between the 10th to the <50th centile (P <0.001). However, rates of neonatal death among live births between >90th centile and the 97th centile of the INTERGROWTH and Canadian criteria were similar (P = 0.46), while neonatal death rates were significantly lower among live births >97th centile of the INTERGROWTH criteria as compared with the Canadian criteria (P = 0.02, Fig 1). Rates of specific severe neonatal morbidity and composite neonatal mortality/morbidity followed a similar pattern (Table 2 and Fig 1).

Table 3 shows the frequency and composite neonatal morbidity/mortality rates in the different centile categories among live births at 33–36 weeks and 37–42 weeks gestation. The left-shift in the frequency of live births when centiles were based on INTERGROWTH criteria

Table 2. Neonatal mortality and morbidity rates (per 1,000 live births) among birth weight-for-gestational age centile categories of the INTERGROWTH-21st Project standard and the Canadian reference, Canada, 2002–12.

Period/ Standard or reference	All live births		<3 rd centile		3 rd -<10 th centile		10 th -<50 th centile		50 th -90 th centile		>90 th -97 th centile		>97 th centile	
	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
<u>INTERGROWTH standard</u>														
Neonatal death	1,423	0.52	226	9.46	140	1.97	392	0.58	447	0.34	112	0.29	106	0.40
Seizures	3,618	1.31	101	4.23	147	2.06	968	1.44	1,524	1.15	460	1.18	418	1.58
Ventilation	18,236	6.99	595	24.9	867	12.2	5,162	7.67	8,511	6.40	2,212	5.66	1,889	7.12
Vent. inc CPAP	42,854	15.6	995	41.7	1,719	24.1	10,943	16.3	19,332	14.5	5,307	13.6	4,558	17.2
Birth asphyxia	15,196	5.52	366	15.3	717	10.1	4,269	6.34	6,535	4.91	1,851	4.74	1,458	5.50
Severe morb/mort.	35,249	12.8	1,108	46.4	1,642	23.0	9,577	14.2	15,313	11.5	4,176	10.7	3,433	12.9
<u>Canadian reference</u>														
Neonatal death	1423	0.52	292	4.67	186	1.08	461	0.43	357	0.31	68	0.32	58	0.59
Seizures	3,618	1.31	184	2.94	284	1.65	1,333	1.25	1,342	1.17	273	1.29	202	2.06
Ventilation	19,236	6.99	987	15.8	1,630	9.49	7,168	6.72	7,093	6.21	1,393	6.58	965	9.86
Vent. incl. CPAP	42,854	15.6	1,775	28.4	3,320	19.3	15,728	14.7	16,438	14.4	3,362	15.9	2,230	22.8
Birth asphyxia	15,196	5.52	762	12.2	1,371	7.98	5,958	5.58	5,407	4.73	1,064	5.03	634	6.48
Severe morb/mort.	35,249	12.8	1,933	30.9	3,048	17.7	13,348	12.5	12,766	11.2	2,530	12.0	1,623	16.6

Vent. incl. CPAP denotes assisted ventilation including continuous positive airway pressure, while severe morb/mort denotes composite severe neonatal morbidity or neonatal mortality. Composite severe neonatal morbidity/mortality included neonatal seizures, assisted ventilation, birth asphyxia, and neonatal mortality.

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compared with the Canadian criteria was observed in both categories of gestational age. Among live births at 33–36 weeks, rates of composite neonatal morbidity/mortality were non-significantly higher in all centile categories under INTERGROWTH criteria except for the large-for-gestational centile categories; composite neonatal mortality/morbidity rates were non-significantly lower in the 90th to 97th centile category and significantly lower in the >97th centile category under the INTERGROWTH criteria compared with the Canadian criteria ($P < 0.001$, Table 3). Patterns of composite neonatal morbidity/mortality among live births 37–42 weeks gestation were similar to overall patterns (Table 2), with higher rates of morbidity/mortality in the small-for-gestational age centile categories under INTERGROWTH criteria and higher rates of morbidity/mortality in the large-for-gestational age centile categories under Canadian criteria. Morbidity/mortality rate differences between centile categories (e.g., <3rd centile vs 50–90th centile) were larger at 37–42 weeks than at 33–36 weeks under both INTERGROWTH and Canadian criteria (Table 3).

Table 4 highlights differences in severe neonatal morbidity/mortality within centile categories of the INTERGROWTH and Canadian criteria. Among all live births, infants <3rd centile of the INTERGROWTH criteria had a rate of composite neonatal morbidity/mortality that was 4.03 times higher (95% CI 3.80–4.28) than the same rate among live births in the 50th to 90th centile of the same criteria. In contrast, there was a 2.77 (95% CI 2.64–2.90) times higher rate of composite severe neonatal morbidity/mortality among live births <3rd centile compared with live births in the 50th to 90th centiles of the Canadian criteria. This difference in rate ratios was reversed in contrasts between rates of composite neonatal morbidity/mortality among large-for-gestational age infants vs infants in the 50th to 90th centile category; the rate ratio among all live births contrasting composite neonatal morbidity/mortality rates among those >97th centile vs those in the 50th-90th centile of the INTERGROWTH criteria was 1.12 (95% CI 1.08–1.17), while the same rate ratio with centiles based on the Canadian criteria was

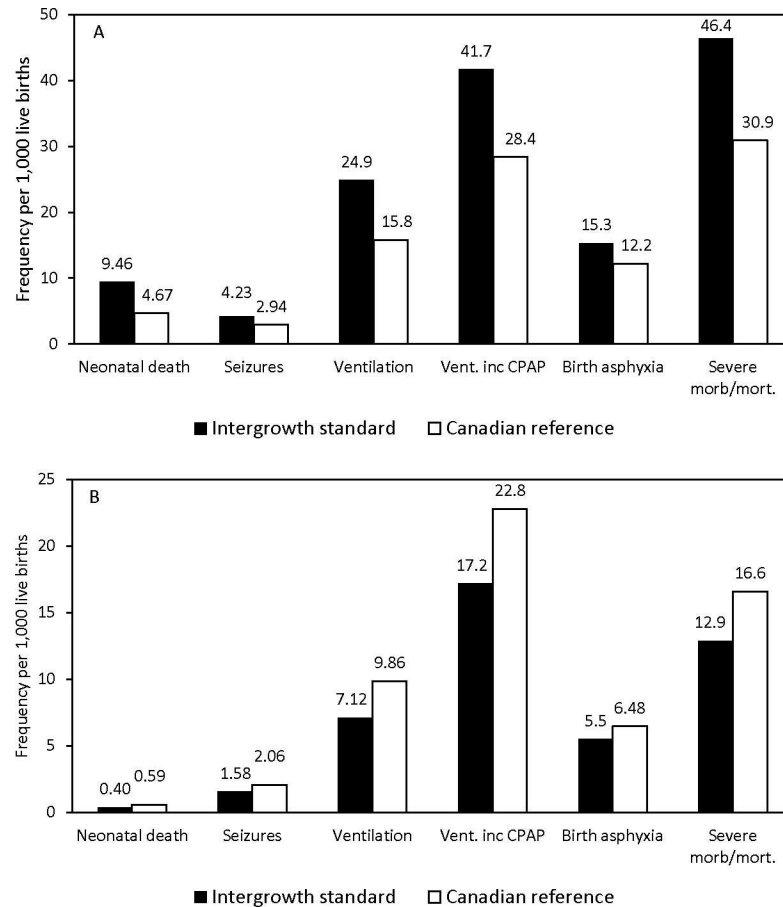


Fig 1. Rates of severe neonatal morbidity and neonatal death among live births <3rd centile (Panel A) and >97th centile (Panel B) of the INTERGROWTH-21st Project newborn birth weight-for-gestational age standard and the Canadian reference, Canada (excluding Quebec) 2002–2012. Vent. inc CPAP denotes assisted ventilation including continuous positive airway pressure and severe morb/mort. denotes composite severe neonatal morbidity and neonatal mortality.

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1.48 (95% CI 1.41–1.56). [Table 4](#) also shows similar patterns in contrasts between the INTERGROWTH and Canadian criteria for high and low risk infants.

The detection (sensitivity) rates of the INTERGROWTH criteria by centile category showed that 3.14% and 7.80% of all cases of composite neonatal morbidity/mortality occurred among live births <3rd centile and <10th centile, respectively, while 5.48% and 14.1% of composite neonatal morbidity/mortality occurred among live births <3rd centile and <10th centile of the Canadian criteria ([Table 4](#)). However, the detection rates of the >97th centile category (9.74%) and the >90th centile category (21.5%) under the INTERGROWTH criteria were higher than the detection rates of the >97th centile category (4.60%) and the >90th centile category (11.8%) under the Canadian criteria. Similar patterns were evident in comparisons of detection rates by centile categories in low- and high-risk populations ([Table 4](#)) and among infants in the 33–36 week and 37–42 week categories ([Table 3](#)).

Discussion

Our study shows that the normative centile distribution of the INTERGROWTH birth weight-for-gestational age standard [1] is left-shifted compared with the Canadian reference [5]. The

Table 3. Rates of composite severe neonatal morbidity/mortality and prognostic performance of the INTERGROWTH-21st Project standard and the Canadian reference among all live births and among low and high risk infants, Canada, 2002–12.

Gestational age category and centile group	INTERGROWTH standard				Canadian reference				INTERGROWTH vs. Canadian criteria	
	Frequency		Composite morbidity and mortality/1000		Frequency		Composite morbidity and mortality/1000		Rate ratio (95% CI)	P value
	No.	Rate	No.	Rate	No.	Rate	No.	Rate		
33–36 weeks	146,669	100.0	8,056	54.9	146,669	100.0	8,056	54.9	-	-
<3 rd	2,816	1.92	263	93.4	3,759	2.56	348	92.6	1.01 (0.87–1.18)	0.91
3 rd to <10 th	5,629	3.84	408	72.5	10,191	6.95	698	68.5	1.06 (0.94–1.19)	0.35
10 th to <50 th	40,602	27.7	2,207	54.4	57,393	39.1	3,044	53.0	1.02 (0.97–1.19)	0.37
50 th to 90 th	72,225	49.2	3,824	52.9	59,100	40.3	3,011	50.9	1.04 (0.99–1.09)	0.10
>90 th to <97 th	14,894	10.2	745	50.0	10,581	7.21	562	53.1	0.94 (0.85–1.05)	0.27
>97 th	10,503	7.16	609	58.0	5,643	3.85	392	69.5	0.83 (0.74–0.94)	0.004
37–43 weeks	2,607,148	100.0	27,193	10.4	2,607,148	100.0	27,193	10.4		
<3 rd	21,069	0.81	845	40.1	58,799	2.26	1,585	27.0	1.49 (1.37–1.61)	<0.0001
3 rd to <10 th	65,608	2.52	1,234	18.8	161,619	6.20	2,350	14.5	1.29 (1.21–1.38)	<0.0001
10 th to <50 th	632,717	24.3	7,370	11.6	1,009,879	38.7	10,304	10.2	1.14 (1.11–1.18)	<0.0001
50 th to 90 th	1,257,474	48.2	11,489	9.14	1,083,474	41.6	9,755	9.00	1.01 (0.99–1.04)	0.28
>90 th to <97 th	375,577	14.4	3,431	9.14	201,153	7.72	1,968	9.78	0.93 (0.88–0.99)	0.01
>97 th	254,703	9.77	2,824	11.1	92,224	3.54	1,231	13.3	0.83 (0.78–0.89)	<0.0001

Composite neonatal morbidity/mortality included neonatal seizures, assisted ventilation, birth asphyxia, and neonatal mortality.

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proportion of Canadian live births deemed to be small-for-gestational age by INTERGROWTH criteria is lower than the proportion identified as small-for-gestational age by the Canadian criteria, while the proportion of live births classified as large-for-gestational age is substantially higher under INTERGROWTH criteria. Differences in neonatal morbidity and mortality rates within centile categories of the INTERGROWTH and Canadian criteria are a product of the left shift in birth weight-for-gestational age centiles of the INTERGROWTH standard. Since small-for-gestational age live births identified by the INTERGROWTH criteria represent more severely growth-restricted infants, their neonatal morbidity/mortality profile is worse than that of small-for-gestational age infants identified by the Canadian criteria. Conversely, the relatively less stringent INTERGROWTH criteria for identifying large-for-gestational age infants resulted in relatively low neonatal morbidity/mortality rates among such infants. Under the normative premise of the INTERGROWTH standard, this overall picture suggests that Canadian live births have low rates of growth restriction and high rates of excess growth. Given the similarity of the Canadian birth weight-for-gestational age reference to the references of other high income countries, it is probable that these findings apply to most industrialized countries.

A large study size and a validated data source are important strengths of our study. Limitations include potential errors with regard to gestational age which would have affected birth weight-for-gestational age centiles under both the INTERGROWTH and Canadian criteria. Although most women in Canada have ultrasound-confirmed gestational age, some errors are inevitable in chart abstraction and transcription. The results of analyses among 33–36 week infants were influenced by the choice of neonatal morbidity (diseases of late gestation which are more influenced by growth restriction [9]), and also by the relatively smaller numbers of such infants. Some transcription errors are also possible with regard to the diagnoses of severe

Table 4. Rates of composite severe neonatal morbidity/mortality and prognostic performance of the INTERGROWTH-21st Project standard and the Canadian reference among all live births and among low and high risk infants, Canada, 2002–12.

Infant group and category	INTERGROWTH standard				Canadian reference			
	Morbidity/mortality rate	Rate ratio*	95% CI	Detection rate (%)†	Morbidity/mortality rate	Rate ratio*	95% CI	Detection rate (%)†
All live births								
<3 rd centile	46.4	4.03	3.80–4.28	3.14	30.9	2.77	2.64–2.90	5.48
3 rd -<10 th centile	23.0	2.00	1.90–2.10	4.66	17.7	1.59	1.53–1.65	8.65
10 th -<50 th centile	14.2	1.24	1.20–1.27	27.2	12.5	1.12	1.09–1.15	37.9
50 th -90 th centile	11.5	1.00	-	43.4	11.2	1.00	-	36.2
>90 th -97 th centile	10.7	0.93	0.90–0.96	11.8	11.9	1.07	1.03–1.12	7.18
>97 th centile	12.9	1.12	1.08–1.17	9.74	16.6	1.48	1.41–1.56	4.60
Infants affected by maternal hypertensive disorders								
<3 rd centile	74.1	6.59	4.55–9.55	6.19	79.4	7.29	5.52–9.63	11.0
3 rd -<10 th centile	79.2	7.05	5.33–9.34	10.7	77.3	7.09	5.63–8.93	16.0
Infants of mothers with gestational diabetes								
>90 th -97 th centile	22.6	2.33	1.90–2.86	13.0	34.6	3.18	2.63–3.85	14.6
>97 th centile	37.7	3.36	2.96–3.81	34.2	40.3	3.70	3.18–4.30	23.3
Infants of diabetic mothers								
>90 th -97 th centile	34.9	3.11	2.40–4.02	11.6	37.8	3.47	2.72–4.42	13.0
>97 th centile	50.6	4.50	3.96–5.12	46.1	55.9	5.13	4.43–5.93	36.0
Infants without slow growth/malnutrition or maternal hypertension/diabetes								
<3 rd centile	39.7	3.53	3.21–3.89	1.33	23.6	2.16	2.02–2.31	2.86
3 rd -<10 th centile	19.1	1.70	1.59–1.81	3.08	15.5	1.43	1.36–1.49	7.22
10 th -<50 th centile	13.5	1.20	1.17–1.23	27.3	12.1	1.11	1.08–1.14	39.8
50 th -90 th centile	11.2	1.00	-	46.4	10.9	1.00	-	38.7
>90 th -97 th centile	10.4	0.93	0.89–0.96	12.6	11.4	1.04	1.00–1.09	7.40
>97 th centile	11.6	1.03	0.99–1.07	9.27	14.1	1.29	1.22–1.37	4.01

* Infants in the 50th to 90th centile category served as the reference group for all live births, while infants without slow growth/ malnutrition or maternal hypertension/diabetes who were in the 50th to 90th centile category served as the reference group for all other rate ratio calculations.

† Detection (sensitivity) rate refers to the proportion of composite neonatal morbidity/morbidity that occurred in that centile category.

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neonatal morbidity. On the other hand, previous studies [7] have shown that the database information is valid, and all diagnoses and procedures were coded using the same system (ICD-10CA and CCI) during the study period. Other study limitations include an evaluation restricted to birth weight-for-gestational age, whereas the INTERGROWTH standard (but not the Canadian reference) included other anthropometric measurements.

Significant changes in the frequency of small-for-gestational age (<3rd and <10th centile) and large-for-gestational age (>97th and >90th centile) live births would occur if the INTERGROWTH standard replaced the Canadian reference (assuming the centile cutoffs for identifying these high risk subpopulations remained unchanged). Another important finding of our study is the decline in rates of severe neonatal morbidity and neonatal death with increasing birth weight-for-gestational age from the <3rd centile category to the >90-97th centile category. In fact, this decline in perinatal morbidity/mortality with increasing birth weight-for-gestational age centile has been demonstrated in numerous previous studies [10–17] and supports the case for an outcome-based determination of INTERGROWTH centile cut-offs for surveillance and monitoring of abnormal growth [18]. The identification of optimal cut-offs for identifying infants at high risk for adverse outcomes needs to balance the proportion of

severe neonatal morbidity and neonatal death identified by the cut-off (sensitivity) with the proportion of infants deemed to be high risk (stratification capacity [8]). The optimal INTERGROWTH standard centile cut-offs for identifying small- and large-for-gestational age live births will likely be resource/cost dependent and hence spatio-temporally specific.

The INTERGROWTH-21st Project suggests that normative standards based on healthy fetuses and newborns are universal and do not need to be customized by ethnicity [4]. Although this conclusion has been criticised [19–22], the INTERGROWTH-21st Project findings are compelling because of the meticulous design and rigorous analysis and also because observed differences in between-country and ethnic-specific fetal growth references potentially reflect differences in maternal socioeconomic status and health [23–25]. Most references are based on populations that include fetuses from complicated pregnancies and fetuses with congenital anomalies, which can exacerbate between country and ethnic-specific differences. The consistency between the INTERGROWTH-21st Project standards [1,2] and the WHO Child Growth Standard [3] at birth, and the lack of ethnic-specific differences in fat free measures of newborn size [1,2] also support the concept of a common universal standard. However, the specific centile cut-offs to be used for designating fetuses/newborns as high-risk in any population will need to be determined on an ad hoc basis through a methodology that balances risks, costs and benefits of antenatal and postnatal screening and the resources required for monitoring high-risk subpopulations. Even if the centile cut-offs used to designate abnormal growth vary by country and ethnicity, use of a common standard (i.e., INTERGROWTH) could help standardize fetal and newborn growth assessment and potentially delineate between-country and ethnic-specific differences.

One finding of note was the poor prognostic performance of the small-for-gestational age and large-for-gestational age centiles of both the INTERGROWTH standard and the Canadian reference for identifying infants at high risk for severe neonatal morbidity and neonatal death. Only 7.8% of infants with composite severe neonatal morbidity/mortality were identified by the small-for-gestational age (<10 centile) category of the INTERGROWTH standard, while the Canadian reference identified 14.1% of such infants as small-for-gestational age (<10th centile, Table 4). The sensitivity rates in the large-for-gestational age category were equally poor, with INTERGROWTH criteria >90th centile identifying 21.5% and Canadian criteria identifying 11.8% of composite neonatal morbidity/mortality. These low sensitivity rates are accompanied by low rates of severe neonatal morbidity/mortality in the <3rd, <10th, >90th and >97th centile categories of both the INTERGROWTH standard and the Canadian reference. The latter implies poor specificity (i.e., a high false positive rate since most infants <3rd centile did not suffer severe neonatal morbidity/death). Growth centiles are perhaps best viewed as one input for use in multivariable models for the screening and identification of high risk infants. Obstetric intervention for abnormal fetal growth is ideally guided by multivariable models that include fetal growth centiles and other risk factors such as uterine and middle cerebral artery blood flow [26–28].

We evaluated the INTERGROWTH newborn standard using a population-based cohort of live births and our findings are likely generalizable to other high income countries with similar birth weight-for-gestational age profiles. It is also likely that our findings and inferences regarding the INTERGROWTH birth weight-for-gestational age standard apply equally to the INTERGROWTH (ultrasound) fetal growth standard [29]. In fact, a case could be made for using the centiles for identifying small- and large-for-gestational age infants (determined through the outcome-based methods proposed above) for fetuses as well since outcome-based determination of biometric centiles for identifying high risk fetuses will be challenging for various reasons including the multiplicity of fetal measurements.

Conclusion

Adopting the INTERGROWTH-21st Project newborn standard using traditional centile cut-offs for identifying abnormal growth will lead to substantial changes in the identification of small-for-gestational age and large-for-gestational age infants in Canada. Although widespread adoption of the INTERGROWTH standards will standardize fetal and newborn growth assessment, further outcome-based research is required to define the appropriate INTERGROWTH centiles for identifying abnormally growth in fetuses and infants that require increased clinical monitoring and surveillance. Multivariable prognostic models based on INTERGROWTH centiles and other factors indicating fetal and infant well-being should be developed for better assessing fetal and infant health status.

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