Original Article

Creation and Validation of the Singapore Birth Nomograms for Birth Weight, Length and Head Circumference Based on a 12-year Birth Cohort

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Abstract

Introduction: Both gestation and birth weight have significant impact on mortality and morbidity in newborn infants. Nomograms at birth allow classification of infants into small for gestational age (SGA) and large for gestational age (LGA) categories, for risk stratification and more intensive monitoring. To date, the growth charts for preterm newborn infants in Singapore are based on the Fenton growth charts, which are constructed based on combining data from various Western growth cohorts. Hence, we aim to create Singapore nomograms for birth weight, length and head circumference at birth, which would reflect the norms and challenges faced by local infants. Materials and Methods: Growth parameters of all babies born or admitted to our unit from 2001 to 2012 were retrieved. Following exclusion of outliers, nomograms for 3 percentiles of 10th, 50th, and 90th were generated for the gestational age (GA) ranges of 25 to 42 weeks using quantile regression (QR) combined with the use of restricted cubic splines. Various polynomial models (second to third degrees) were investigated for suitability of fit. The optimum QR model was found to be a third degree polynomial with a single knotted cubic spline in the mid-point of the GA range, at 33.5 weeks. Check for goodness of fit was done by visual inspection first. Next, check was performed to ensure the correct proportion: 10% of all cases fall above the upper 90th percentile and 10% fall below the lower 10th percentile. Furthermore, an alternative formula-based method of nomogram construction, using mean, standard deviation (SD) and assumption of normality at each gestational age, was used for counterchecking. Results: A total of 13,403 newborns were included in the analysis. The new infant-foetal growth charts with respect to birth weight, heel-crown length and occipitofrontal circumference from 25 to 42 weeks gestations with the 10th, 50th and 90th were presented. Conclusion: Nomograms for birth weight, length and head circumference at birth had significant impact on neonatal practice and validation of the Singapore birth nomograms against Fenton growth charts showed better sensitivity and comparable specificity, positive and negative predictive values.

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Key words: Fenton, Percentile, Prematurity, Preterm growth charts, Very low birth weight

Introduction

Both gestation and birth weight have significant impact on mortality and morbidity in newborn infants.[1,2] Nomograms at birth allow classification of infants into small for gestational age (SGA) and large for gestational age (LGA) categories, based on <10th percentile and >90th percentile birth weights respectively. These categorisations allow for risk stratification and more intensive monitoring.

A recent review stated that uncertainty existed regarding the most suitable curves for monitoring the growth of preterm infants. While intrauterine growth rate appeared to be the ideal growth that needs to be attained by the preterm infants, there were considerable problems with its accuracy and it may not be feasible to attain such growth trajectories, given the limitations set by the morbidities of prematurity.[3] Bertino et al also stated in a review on neonatal charts that localised or national growth charts were preferred by clinicians, and that these should be descriptive "how growth actually is" serving as a reference, and should be updated every 5 to 10 years or at the most 15 to 20 years.[4] However, the last

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published growth charts for Singapore was in 1972 and in 1994 for Malaysia.[5,6]

Currently, most neonatal centres use variations of charts developed by Babson and Benda, Lubchenco or Usher.[3] The Babson and Benda's chart, which was 4 decades old, had been updated by Fenton, using recent data from larger samples of preterm infants, making it useful for monitoring growth of infants in the preterm period.[7,8] Once a corrected age of 40 weeks is reached, the appropriate paediatric growth curves can be used to monitor their ongoing growth.

To date, the growth charts for newborn infants in Singapore are based on the Fenton growth charts, which are constructed based on combining data from various Western growth cohorts from the 1990s.

Our study aimed to create updated Singapore birth nomograms for birth weight, length and head circumference at birth, which would reflect the norms and challenges faced locally.

Materials and Methods

Growth parameters of all babies born or admitted to our unit from 2001 to 2012 were included. Babies with major congenital malformations were excluded. Gestational age (GA) by completed weeks was determined by early ultrasound dating or by last menstrual period. If the gestation was less than 37 weeks, it was counterchecked with the Dubowitz or new Ballard scoring post-delivery. Where Dubowitz or Ballard scoring differed by more than 2 weeks from the last menstrual period and in the absence of early dating scans, the Dubowitz- or Ballard-scored GA was taken.

All parameters were measured immediately after birth or at the latest, within 24 hours after birth. Birth weight was taken using digital weighing scales accurate to the nearest gram, after the baby was dried. Head circumference was taken by using the occipitofrontal circumference with a measuring tape. Length was taken with a stadiometer, as part of the weighing scale, using heel-crown length. Measurements were rounded to the nearest centimetre.

Possible erroneous data entry, measurement or recording of birth weight, head circumference and crown-heel length were identified in 2 ways. First, visual inspection of box -and-whisker plots of each live birth measurement by GA identified obvious implausible data points. Next, the statistical method of Tukey[9] was used to discard outliers, because the large volume of birth data made it impossible to trace every single suspicious data from the visual examination of box-and-whisker plot. Tukey's method consisted of computing the 25th and 75th percentiles for each GA to get the interquartile range (IQR), IQR being 75th percentile to 25th percentile. Within each GA, data points higher than 1.5 multiples of IQR from the 75th percentile or lower than 1.5 multiples of IQR from 25th percentile were discarded and not used in the construction of birth nomograms.

Following exclusion of these outliers, nomograms for 3 percentiles of 10th, 50th, and 90th were generated for the GA range of 25 to 42 weeks using quantile regression (QR) combined with the use of cubic splines[10] for each type of measurement. Various polynomial models (second to third degrees) were investigated for suitability of fit to the data. The optimum QR model for the 3 types of live-birth measurements was found to be a third degree polynomial in terms of GA (i.e. a model with linear, quadratic and cubic terms of gestational age) with a single knotted cubic spline in the mid-point of the GA range, at 33.5 weeks. Such a knot was chosen to allow for some change in growth curve direction halfway through the GA range that was observed from the empirical data plotted on a graph.

Check for goodness of fit model was done by visual inspection of the nomograms with the empirical data superimposed on the nomograms. Next, check was performed that approximately the correct proportion of 10% of all cases fall above the upper 90th percentile and 10% of all cases fall below the lower 10th percentile. Furthermore, an alternative simple method of nomograms construction was used for counter-checking, not based on modeling technique, but by formula based on mean and standard deviation (SD) and assumption of normality at each integer GA. For example, the 10th and 90th percentile at a particular GA was calculated respectively as mean — $Z_{0.90}$*SD, mean + $Z_{0.90}$*SD, where mean and SD are the values at corresponding GA, $Z_{0.90}$ is the z-score value corresponding to an area of 0.9 under the standard normal curve to the left of that z-score ($Z_{0.90}$ = 1.28). To obtain any particular centile curve by this method, the centile points for the GAs were connected smoothly by the use of third degree polynomial functions using Excel graphing capabilities. A visual check was then made of how closely the nomograms constructed by QR and simplistic formula based on mean and SD at each GA coincide.

Comparison between the Fenton growth charts and Singapore birth nomograms were performed using SGA clinical outcomes to obtain sensitivity, specificity, positive and negative predictive values. SGA morbidities were defined as one or all of the following: perinatal depression, meconium aspiration, pulmonary haemorrhage, persistent pulmonary hypertension of newborn, hypotension, hypoglycaemia, hypocalcemia, hypothermia, polycythaemia, neutropenia, thrombocytopenia and renal insufficiency.[11] Perinatal depression was defined as Apgar scores at 5 minutes of 5 and below. Persistent pulmonary hypertension of newborn (PPHN) was diagnosed by echocardiography performed by paediatric cardiologists. 2D echocardiography was

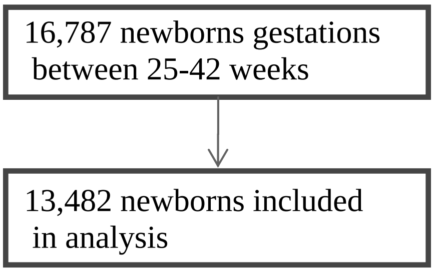

Fig. 1. The dataset was cleaned up with outliers at each gestation group removed by Tukey's method (more than 1.5 boxlength away from 25th or 75th percentile) for birth weight, length and head circumference. Outliers were removed for birth weight, length and head circumference numbered 322, 271 and 580 respectively. Head circumference measurement was missing for 2530 patients before clean-up. The number of missing data for birth weight was 1 and for length it was 72. As we wanted a clean-up dataset with complete data and equal final samples for all 3 measurements, this resulted in 3300 newborns being excluded.

Table 1. Baseline Characteristics

Characteristics	Frequency (%)
25	27 (0.20)
26	34 (0.25)
27	58 (0.43)
28	71 (0.53)
29	86 (0.64)
30	101 (0.75)
31	100 (0.74)
32	144 (1.07)
33	188 (1.39)
34	283 (2.10)
35	352 (2.61)
36	833 (6.18)
37	1680 (12.46)
38	3234 (23.99)
39	3414 (25.32)
40	2366 (17.55)
41	456 (3.38)
42	55 (0.41)
Gender	
Male	6973 (51.72)
Female	6509 (48.28)
Ethnic Group	
Chinese	6055 (44.97)
Malays	5189 (38.53)
Indians	1309 (9.72)
Others	913 (6.78)
Multiple Births	
Singletons	12,909 (95.75)
Twins	518 (3.84)
Triplets	55 (0.41)

not performed for all babies, except only when clinical suspicion of PPHN existed. Hypotension was defined as mean arterial blood pressure less than GA. Hypothermia was defined as axillary temperature less than 36.5 ˚C, hypoglycemia as plasma glucose level of less than or equal to 2.5 mmol/L and hypocalcemia as plasma total calcium level <2.0 mmol/L or ionic calcium level <1.0 mmol/L. In addition, renal insufficiency was assessed clinically by oliguria and/or if the urea, creatinine tests performed were abnormal. All premature babies defined as less than 37 weeks gestation, whether SGA or non-SGA, would undergo the same clinical and blood tests monitoring in terms of full blood count, serum calcium and blood sugar monitoring regime for the first 24 hours. In term babies, only SGA babies who were low birth weight (less than 2500 g) would have the blood tests monitoring performed, although clinical monitoring were similar.

Results

Figure 1 shows the flowchart for patient inclusion, while Table 1 shows the baseline characteristics of infants included in the analysis. Tables 2, 3 and 4 shows the 10th%, 50th% and 90th% values for the birth weight, head circumference and length respectively. Figures 2, 3 and 4 are diagrammatic representations of the 10th%, 50th% and 90th% values for the birth weight, head circumference and length respectively.

Clinical Validation and Comparisons Between the Fenton Growth Charts and Singapore Birth Nomograms Using SGA Morbidities

Tables 5 and 6 compared the use of the Singapore birth nomogram against the Fenton growth chart, as screening tools for SGA morbidities, when validated against the birth cohort from 2001 to 2012.

Further counter-checking was performed by performing chi-square test for mortality against gestation and against weight percentiles for GA. Statistical significance was found in mortality against gestation ($P < 0.001$) [n (%) for mortality in gestation age groups ≤37 weeks, 38-41 weeks, ≥42 weeks were 18 (0.46%) versus 0 (0%) versus 0 (0%) respectively], while no statistical significance was found against weight percentiles for GA ($P = 0.614$) [n (%) for mortality in SGA, AGA and LGA were 3 (0.22%) versus 13 (0.12%) versus 2 (0.15%)].

Discussion

In the 1960s, Battaglia et al[12] published a study on birth weights against gestational age from John Hopkins Hospital, while Lubchenco et al[13] published birth weight against GA distribution from Colorado involving both inborn and

Table 2. Birth Weight Data (in Grams) Used for Constructing Singapore Birth Nomogram Using QR

GA	Mean	SD	Frequency	QR 10th%	QR 50th%	QR 90th%
25	719.6	91.67	27	602.2	775.0	991.3
26	880.9	166.84	34	620.0	845.0	1032.1
27	972.5	164.47	58	671.6	942.3	1130.0
28	1006.3	252.50	71	755.0	1064.6	1276.4
29	1206.5	215.20	86	867.4	1209.7	1462.6
30	1365.2	228.32	101	1005.9	1375.4	1680.0
31	1548.9	284.46	100	1167.7	1559.6	1920.1
32	1734.3	377.91	144	1350.1	1760.0	2174.2
33	1950.4	350.26	188	1550.2	1974.5	2433.8
34	2236.5	436.66	283	1765.0	2200.6	2690.2
35	2453.4	338.52	352	1987.5	2431.7	2935.9
36	2696.7	402.33	833	2206.7	2656.9	3164.7
37	2893.2	352.63	1680	2441.3	2865.0	3370.0
38	3065.9	387.08	3234	2590.0	3045.0	3545.6
39	3187.0	381.88	3414	2731.7	3185.7	3685.0
40	3297.0	363.82	2366	2825.0	3276.1	3781.9
41	3347.6	380.37	456	2858.8	3305.0	3830.0
42	3384.4	518.86	55	2821.8	3261.3	3822.8

GA: Gestational age; QR: Quantile regression; SD: Standard deviation

Table 3. Head Circumference Data (in Centimetres) Used for Constructing Singapore Birth Nomogram Using QR

GA	Mean	SD	Frequency	QR 10th%	QR 50th%	QR 90th%
25	22.4	0.84	27	22.0	23.0	24.0
26	24.1	1.52	34	21.9	23.3	25.3
27	24.8	1.36	58	22.3	24.0	26.6
28	25.0	1.85	71	23.0	24.9	27.8
29	26.6	1.50	86	24.0	26.1	29.0
30	27.6	1.62	101	25.1	27.3	30.0
31	28.7	1.47	100	26.4	28.6	31.0
32	29.6	1.83	144	27.7	29.9	31.9
33	30.7	1.63	188	28.9	31.0	32.7
34	31.8	1.53	283	30.0	32.0	33.4
35	32.5	0.95	352	31.0	32.7	34.0
36	33.2	1.17	833	31.8	33.3	34.5
37	33.6	0.90	1680	32.4	33.6	35.0
38	33.9	1.14	3234	32.8	33.8	35.4
39	34.0	1.08	3414	33.0	34.0	35.7
40	34.3	0.94	2366	33.0	34.0	35.9
41	34.4	0.95	456	32.8	34.0	36.0
42	34.6	0.94	55	32.3	33.9	36.0

GA: Gestational age; QR: Quantile regression; SD: Standard deviation

Table 4. Length Data (in Centimetres) Used For Constructing Singapore Birth Nomogram by QR

GA	Mean	SD	Frequency	QR 10th%	QR 50th%	QR 90th%
25	32.6	1.25	27	31.0	33.0	35.6
26	34.8	2.56	34	31.3	34.3	37.0
27	35.8	2.27	58	32.0	35.7	38.5
28	36.4	3.18	71	33.1	37.1	40.0
29	38.4	2.58	86	34.5	38.6	41.5
30	39.9	2.17	101	36.0	40.0	43.0
31	41.2	2.62	100	37.7	41.4	44.4
32	42.3	2.73	144	39.4	42.7	45.7
33	43.4	2.30	188	41.0	44.0	46.9
34	44.9	2.45	283	42.5	45.1	47.9
35	46.1	1.74	352	43.8	46.1	48.7
36	47.1	1.77	833	45.0	47.0	49.4
37	47.9	1.68	1680	45.9	47.8	50.0
38	48.5	1.70	3234	46.6	48.4	50.5
39	49.1	1.61	3414	47.0	49.0	51.0
40	49.5	1.57	2366	47.1	49.4	51.5
41	49.7	1.60	456	47.0	49.8	52.0
42	49.7	2.00	55	46.5	50.0	52.6

GA: Gestational age; QR: Quantile regression; SD: Standard deviation

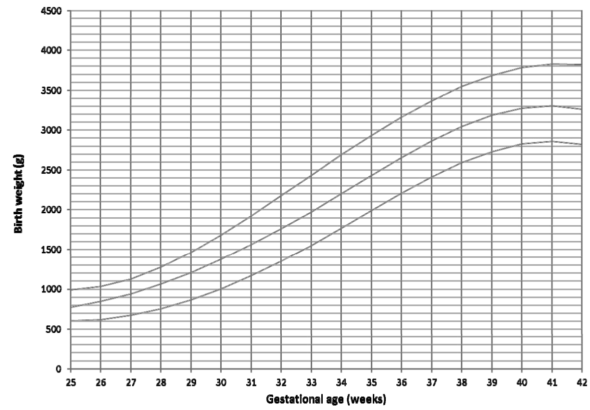

Fig. 2. Chart showing Singapore birth nomogram with 10th, 50th and 90th percentile for birth weight by gestational age.

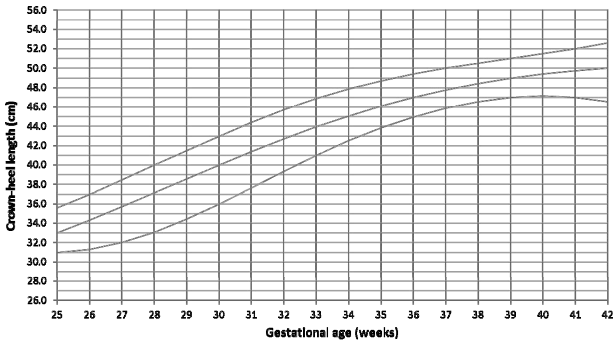

Fig. 4. Chart showing Singapore birth nomogram with 10th, 50th and 90th percentile for crown-heel length by gestational age.

Fig. 3. Chart showing Singapore birth nomogram with 10th, 50th and 90th percentile for head circumference by gestational age.

outborn infants. The two studies, published within a few years of each other, showed remarkable agreement in the 10th percentile of the birth weight against GA plot, but differed markedly in the 90th percentile distribution.[14] Since then, birth nomograms for preterms and terms had significant impact on neonatal practice, particularly if customised for the individual population.[15]

A recent review of mortality rates conducted under the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network employed the approach of these original studies, using birth weight and GA data to construct mortality rates.[16] Unfortunately, the article "did not present the data in a useable format that related mortality to both gestational age and birth weight.

Table 5. SGA Morbidities Using Singapore Birth Nomograms

GA	SGA	None-SGA	Percentage SGA	True Positive	False Positive	True Negative	False Negative	Sensitivity	Specificity
25	6	28	17.65%	6	0	2	26	18.75%	100.00%
26	2	36	5.26%	2	0	10	26	7.14%	100.00%
27	4	58	6.45%	4	0	21	37	9.76%	100.00%
28	10	73	12.05%	9	1	26	47	16.07%	96.30%
29	8	84	8.70%	7	1	43	41	14.58%	97.73%
30	13	99	11.61%	11	2	59	40	21.57%	96.72%
31	9	99	8.33%	6	3	68	31	16.22%	95.77%
32	23	131	14.94%	10	13	82	49	16.95%	86.32%
33	27	178	13.17%	10	17	111	67	12.99%	86.72%
34	44	261	14.43%	15	29	180	81	15.63%	86.12%
35	44	394	10.05%	21	23	296	98	17.65%	92.79%
36	117	804	12.70%	37	80	629	175	17.45%	88.72%
37	243	1957	11.05%	65	178	1715	242	21.17%	90.60%
38	356	3613	8.97%	62	294	3284	329	15.86%	91.78%
39	429	3895	9.92%	53	376	3637	258	17.04%	90.63%
40	320	2724	10.51%	46	274	2515	209	18.04%	90.18%
41	64	553	10.37%	8	56	511	42	16.00%	90.12%
42	10	71	12.35%	1	9	65	6	14.29%	87.84%
Total	1729	15058	10.30%	373	1356	13254	1804	17.13%	90.72%

GA: Gestational age; SGA: Small for gestational age

Table 6. SGA Morbidities Using Fenton Growth Chart

GA	SGA	None-SGA	Percentage SGA	True Positive	False Positive	True Negative	False Negative	Sensitivity	Specificity
25	3	31	8.82%	3	0	2	29	9.38%	100.00%
26	5	33	13.16%	5	0	10	23	17.86%	100.00%
27	4	58	6.45%	4	0	21	37	9.76%	100.00%
28	18	65	21.69%	14	4	23	42	25.00%	85.19%
29	9	83	9.78%	8	1	43	40	16.67%	97.73%
30	21	91	18.75%	15	6	55	36	29.41%	90.16%
31	10	98	9.26%	7	3	68	30	18.92%	95.77%
32	23	131	14.94%	10	13	82	49	16.95%	86.32%
33	23	182	11.22%	8	15	113	69	10.39%	88.28%
34	32	273	10.49%	9	23	186	87	9.38%	89.00%
35	30	408	6.85%	18	12	307	101	15.13%	96.24%
36	69	852	7.49%	25	44	665	187	11.79%	93.79%
37	117	2083	5.32%	40	77	1816	267	13.03%	95.93%
38	208	3761	5.24%	44	164	3414	347	11.25%	95.42%
39	318	4006	7.35%	44	274	3739	267	14.15%	93.17%
40	408	2636	13.40%	54	354	2435	201	21.18%	87.31%
41	144	473	23.34%	12	132	435	38	24.00%	76.72%
42	32	49	39.51%	3	29	45	4	42.86%	60.81%
Total	1474	15313	8.78%	323	1151	13459	1854	14.84%	92.12%

GA: Gestational age; SGA: Small for gestational age

However, the only coloured graph in the study suggested no difference for mortality at gestational ages older than 29 weeks whether the infants were LGA or SGA. There was criticism that comparisons were weakened in terms of clinical usefulness by the inclusion of gender differences as well."[14]

Obstetric research pointed out that foetal growth curves constructed from ultrasonographic estimation of fetal size in normal pregnancies defined greater fetal weights at any given GA than the curves using birth weight data. In addition, it is unclear whether calculating an estimated fetal weight from population-based data of multiple fetal measurements is an improvement over using those measurements themselves to detect undersized infants.[17] Ultrasound estimation of birth weights remain fraught with inaccuracies for various reasons.[18]

Each nation should construct its own birth nomograms, with their own outcomes based on gestation and SGA versus non-SGA subgroups. This can act as a barometer for their obstetric and neonatal practices, assist in prognostication and counseling of parents and finally, serve as a platform to further improve medical practice and outcomes. In this aspect, the United States was first off, having already published their national growth chart based on their multi-ethnic birth cohort.[16] We believe our study contributed to the literature on Asian ethnicity growth for preterm babies and for Singapore, and at the minimum, provided data for future meta-analyses on growth of preterm babies in Asia.

Visual inspection of the Fenton growth charts and Singapore birth nomograms superimposed together (Figs. 5, 6 and 7) reveal that the Fenton growth chart tends to increase in a linear fashion as it goes into the term and post-term gestations. In contrast, the Singapore birth nomograms show a more sigmoidal S-shaped curve. We believe that the latter corroborates with our clinical experience. Newborns do not grow linearly indefinitely while gestation increases; this growth is expected to tail off as the baby reaches term or post-term. This difference between the charts could be due to the artificial amalgamation of different growth cohorts, preterm versus term, in the making of the Fenton growth charts.

In addition to risk stratification, these growth charts were also important for the monitoring of post-natal growth for premature babies. These infants were at risk for poor growth, whether in the hospital or after discharge. They must be closely monitored and may require interventions to promote better growth.

To date, no studies have been performed to validate how the Fenton growth charts performed in a cohort of real patients, in terms of risk stratification. When we validated the Fenton growth charts on our study population, we found that they had high negative predictive values. This corroborated with actual clinical practice as the growth charts were used as the first layer of screening in SGA babies, who were then further screened clinically, as well as with blood investigations such as full blood count, blood sugar monitoring and electrolyte checks.

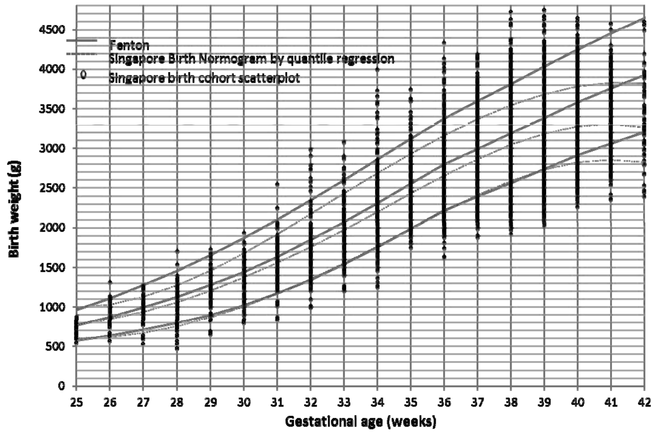

Fig. 5. Chart showing the 10th, 50th and 90th percentiles for birth weight by gestational age.

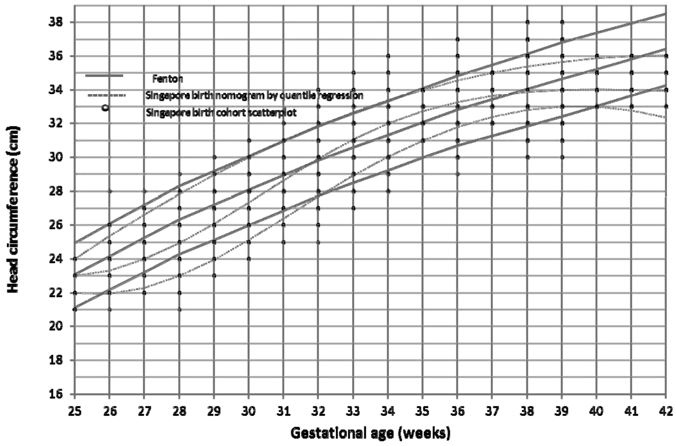

Fig. 6. Chart showing the 10th, 50th and 90th percentiles for head circumference by gestational age.

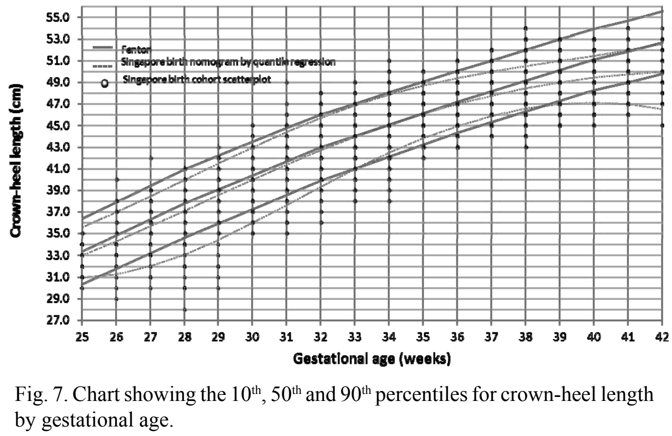

Fig. 7. Chart showing the 10th, 50th and 90th percentiles for crown-heel length by gestational age.

Table 7 summarises the results for Tables 5 and 6 for SGA morbidities screening. Our comparison showed that the Singapore birth nomograms' positive and negative predictive values, as well as specificity, were comparable to the Fenton growth charts. In addition, it had higher sensitivity. We believe this was an important additional advantage as a first line screening tool.

Table 7. PPV, NPV, Sensitivity and Specificity for the Fenton Growth Charts and Singapore Birth Nomograms

Characteristics	Fenton Growth Charts	Singapore Birth Nomograms
PPV	21.91%	21.57%
NPV	87.89%	88.02%
Sensitivity	14.84%	17.13%
Specificity	92.12%	90.72%

NPV: Negative predictive value; PPV: Positive predictive value

Limitations and Future Research

Our cohort may not be representative of the national growth cohort as our centre is only 1 of 3 public tertiary neonatal units, and a substantial proportion of births occur in private centres. However, we believe we have sufficient numbers accumulated over the years to be representative, particularly in the near term and term gestations. In particular, we systematically collected both growth parameters and outcome data prospectively for all babies during admission.

There was over-representation of Malays in our cohort, compared to the ethnic make-up of Singapore. However, Malays had higher fertility rates during the study period compared to other ethnic groups. Malay fertility rate ranged from 1.64 to 2.54 compared to overall population total fertility rate of 1.2 to 1.6. This meant that Malay infants would naturally be over-represented in any local natural birth cohort, as opposed to the general population ethnic make-up. Our construction of separate nomograms for each race also did not show any racial differences.

Head circumference from 39 weeks onwards increased only marginally, for the 50th percentile and 90th percentile curves. We believe that in the future when we have more data at GA 41 and 42 weeks, we will have a more accurate picture of the nomograms at the tail ends of the curves for head circumference. Interestingly, in the Malaysian curves for head circumference by Boo et al,[6] a similar finding of no more than minimal increase was found at the tail ends too.

There was a possibility of inaccuracies in data entry, although data accuracy was counter-checked during data entry. Hence, we employed various statistical means to remove outliers to improve accuracy.

Further research should include a future prospective study to see how well the Singapore birth nomograms fare in picking up both SGA and LGA morbidities in the various gestations. In addition, prospective multi-centre studies could hopefully be performed in future to construct nomograms and see whether and how much these will defer from these currently constructed nomograms. Hopefully, there would also be further research around the world, and particularly in Asia, to obtain norms at birth for different gestations for different nations and ethnic groups.

Conclusion

Not only were the Singapore birth nomograms based on local birth cohort of Asian ethnicity and more recent births, there was also no artificial amalgation of different cohorts across gestations, unlike the Fenton growth charts. Validation of the Singapore birth nomograms against Fenton growth charts showed better sensitivity and comparable specificity, positive and negative predictive values.

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