Pediatric RESEARCH

CLINICAL RESEARCH ARTICLE

Accuracy of preterm infant weight gain velocity calculations vary depending on method used and infant age at time of measurement

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BACKGROUND: We examined preterm infants' weight gain velocity (WGV) to determine how much calculation methods influences actual WGV during the first 28 days of life.

METHODS: WGV methods (Average 2-point, Exponential 2-point, Early 1-point, and Daily) were calculated weekly and for various start times (birth, nadir, regain, day 3 and day 7) to 28 days of age for 103 preterm < 1500 gram infants, with daily weights.

RESULTS: Range of WGV estimates decreased 10–22 g/kg/day to 15.5–15.8 g/kg/day when the Early 1-point method and the postnatal weight loss phase were excluded. WGV were lower when the postnatal weight loss was included and higher using the early method. WGV calculations beginning at day 7 did not differ from calculations beginning at the nadir.

CONCLUSIONS: Variations in WGV calculations were large enough to create difficulties for comparing results between studies and translating research to practice. We recommend that the postnatal weight loss phase be excluded from WGV calculations and clinical studies report weight nadir and weights at day 7 and 28 to allow adequate comparison and translation of findings in clinical practice. The Average2pt method may be easier to calculate at bedside, so we recommend it be used in clinical settings and research summaries. The Early1pt method should not be used to summarize WGV for research.

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INTRODUCTION

Since growth is an indicator of nutritional adequacy and general well-being, health practitioners often report weight gain to 28 days of life as an outcome measure for preterm infants.[1] Clinical growth monitoring is especially important for preterm infants as they depend on health care providers to decide how much nutrition to provide.

The most frequently quoted weight gain velocity (WGV) metric for preterm infants has been grams per kilogram per day (g/kg/day).[1] Forty percent of preterm infant recent research studies reported weight gain as g/kg/day, ahead of the other WGV metrics; grams per day (32%) and changes in z-scores (29%), although z-scores have been gaining popularity in recent years.[1]

The g/kg/day WGV calculation methods used include: aAverage 2-point (Average2pt); Exponential 2-point (Exp2pt); Early 1-point (Early1pt) and Daily (Tables 1).[1,2] This range of preterm infant WGV calculation methods reported in research papers likely reflect the ways growth is calculated clinically.

Most of the published g/kg/day WGV calculations used birthweight as the starting point,[1] even though birth is usually followed by a few days of weight loss before weight gain commences.

Using the various WGV calculation methods and time-intervals, g/kg/day WGV calculations along the 50th centile of frequently used preterm growth charts can range from 8 to 41 g/kg/day.[2] If clinicians are aiming for 15–20 g/kg/day, the reference growth rate of the intrauterine fetuses,[2] they may make incorrect conclusions about infants' growth depending on the calculation method and time-interval used. Whether the actual observed WGV of preterm infants is affected as much by calculation method as theoretical growth along the 50th centile is unknown.

We used frequent anthropometric measurements (daily weight measurements through hospitalization followed by weekly measurements post-discharge) of a cohort of preterm infants born prior to 30 weeks gestational age. Our objective was to examine the variability between the four WGV calculation methods used to summarize the infants' weight gain weekly for the first 21 weeks of life and then between frequently used starting times (birth, weight nadir, days 3 and 7 and when birthweight was regained) to 28 days of life, a commonly used end point for growth calculations in published studies.[1]

METHODS

Daily weight data was collected during the PreM Growth cohort Study[3] of very preterm infants born in 2010–2014 in Calgary Canada. Clinic inclusion criteria were birthweight < 1250 g and/or GA < 29 week's gestation prior to October 2011 and birthweight < 1000 g and/or GA < 29 week's gestation afterwards.

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Table 1. Weight gain calculation methods expressed in grams/kilogram/day (g/kg/day) over a period of time[a]

Daily (Daily)	$\frac{(W_2 - W_1)}{((W_1 + W_2) \div 2) \div 1000}$
Average 2-point average method (Avg2pt)	$\frac{\frac{(W_2 - W_1)}{((W_1 + W_2) \div 2) \div 1000}}{\text{number of days}}$
Early 1-point method (Early1pt)	$\frac{\frac{(W_2 - W_1)}{(W_1) \div 1000}}{\text{number of days}}$
Exponential 2-point method (Exp2pt)	$\frac{\ln\left(\frac{W_2}{W_1}\right) * 1000}{\text{number of days}}$

[a]W_1 and W_2 are initial and final body weight expressed in grams, for the Daily method, W_1 and W_2 are daily weights for two days in sequence

Subjects
Beginning with a convenience sample of 128 infants that fit the inclusion criteria, infants with birthweights below the 10th centile ($n = 14$, 11%) or above the 90th centile ($n = 3$, 2%) for their GA relative to the Fenton 2013 growth chart[4] were excluded since growth patterns differ[5–8] from those with weights appropriate for GA (AGA) and their numbers were too small to be analyzed separately. Eight (7%) infants were also omitted for missing in-hospital weights for greater than 6 continuous days.

Measurements
Anthropometric measurements were made by neonatal nurses during routine neonatal care in hospital and post-discharge in the infants' homes (home measurements were usually done weekly). Weights were measured using electronic scales to the nearest gram. The data were collected from the medical charts and entered into the database by trained neonatal Dietitians. This study was granted ethical approval by the University of Calgary Conjoint Health Research Ethics Board.

Neonatal morbidities were not an exclusion, nor were they controlled for in the analysis, as the primary goal of the study was to assess the effect of calculation method across a wide range of preterm infants. Among the 103 infants in this study, missing weight measures (8% had 1 day missing, 3% were missing 2 days, 1% was missing 6 days) were interpolated linearly using the neighbouring data points, between discharge to postnatal 150 days of life, at which point the data became more intermittent. The weight nadir was the lowest weight in the first 2 weeks of life and the day of regained birthweight was defined as the day after the last day of weight less than birthweight.[5]

The WGV calculations were calculated for each infant using the formulae in Table 1. The effect of the different calculation methods across times and different start times across methods were compared using within-subjects ANOVA or paired *t*-tests using Stata 15.1 (Statacorp College Station TX). Box plots were used to examine the distributions of the WGV results, to examine for violations of the ANOVA analysis.

The median weight gain patterns of sub-cohorts of the infants born at each week of GA were illustrated on the Fenton 2013 girl–boy average growth chart[4] using their completed weeks of gestation and the completed weeks version of the growth chart data. Since the accuracy of the mean of small samples (weekly cohort $n = 2, 16, 13, 13, 22, 26, 11$) was likely poor, as explained by the central limits theorem, the medians were plotted to provide more representative estimates of the mid-points. Exponential curves increasing at 15 and 20 g/kg/day were calculated and superimposed on the weight gain patterns beginning at 23 weeks using the median birthweight (567 grams) of the cohort 23 week infants.

Table 2. Birth and morbidity characteristics of <30 week preterm infants with birthweight appropriate for gestational age

	n	103
	% Male	51
Gestational age	Weeks of gestation	26.9 ± 1.7
Birthweight	Grams	910 ± 203
Birth head circumference	Centimeters	24.6 ± 2.1
Birth length	Centimeters	34.6 ± 3.7
Postnatal weight loss	% weight loss	10.1 ± 4.9
	Day of weight nadir (days)	4.8 ± 1.8
	Weight at nadir (grams)	818 ± 184
	Weight at day 3 (grams)	854 ± 184
	Weight at day 7 (grams)	870 ± 196
	Day of weight regain (days)	12.1 ± 4.7
Morbidities[a]	Bronchopulmonary dysplasia	55 (53%)
	Necrotizing enterocolitis	6 (6%)
	Intraventricular hemorrhage 3+	8 (8%)
	Periventricular leukomalacia	4 (4%)
	Cerebral palsy	4 (4%)
Z-scores[b]	Birthweight	−0.1 ± 0.6
	Weight at nadir (grams)	−0.9 ± 0.5
	Weight at day 7 (grams)	−0.8 ± 0.5
	Weight at 36 weeks	−1.3 ± 0.7
	Weight at 48 weeks	−1.1 ± 1.1
Nutrition care	Day of parenteral nutrition start	0.1 ± 0.2
	Days of parenteral nutrition	23 ± 14
	Day of first minimal enteral feeding	2.0 ± 2.6
	Day of first enteral feeding (≥20 mL/kg)	8.3 ± 6.6
	Day of full enteral feeding (≥140 mL/kg)	24 ± 14
	Predominantly fortified breastmilk	89%

[a]Bronchopulmonary dysplasia was defined when infants were on oxygen support at 36 weeks; necrotizing enterocolitis as Bell's stage 2+
[b]Z-scores relative to the Fenton 2013 growth chart

Data analysis
Adjustment for multiple comparisons were made using a Bonferroni adjustment reduced the starting *p*-value of 0.05 to 0.0012, statistical tests were 2-sided. Absolute percent differences (APD) were calculated by dividing the differences by the average of the two values, then multiplying by 100%. Differences greater than 10% APD were considered clinically significant.

RESULTS

Population demographics
One hundred and three < 1500 gram AGA infants were included in this study. The cohort's birthweight was 910 ± 203 grams (median = 930, range 507–1440) and 63% percent of this cohort had neonatal morbidities (Table 2). Only one infant was lost to follow-up prior to 48 weeks PMA, and that occurred at 42 weeks.

For nutrition care provided to this cohort, parenteral nutrition began for almost all infants on their day of birth (Table 2). Eighty nine percent of the infants were fed fortified own mothers' milk with bovine fortifiers. Dietitians monitored and recommended nutrition care in the neonatal units.

Growth patterns

At birth the sub-cohorts' median weights were close to the medians of the preterm growth charts[4] (Fig. 1), although the 29-week cohort had slightly lower weight z-scores (birthweight z-score = −0.7 ± 0.5) as 29-week infants with higher birthweights were excluded by the clinic's inclusion criteria. After the postnatal weight loss, the median weight gain growth patterns for each sub-cohort were approximately parallel to the growth chart curves. In contrast, the superimposed 15 and 20 g/kg/day exponential curves did not have a nadir below the starting weight similar to a postnatal weight loss in the first week. Subsequent to the postnatal weight loss phase, the 15 g/kg/day exponential curve was approximately parallel initially to the sub-cohort medians, while the 20 g/kg/day curve began diverging upward, crossing the growth chart median curve at 29 weeks. Both the 15 and 20 g/kg/day curves were almost vertical by 41 and 45 weeks, respectively (Fig. 1).

Weight z-scores among this cohort of AGA infants with some morbidities decreased significantly from birth to 7 days to 36 weeks and then increased slightly after 36 weeks (Table 2).

Effect of calculation method for 1-week periods

Weekly WGV were all statistically different across the 4 methods for all of the individual weeks from week 1 to week 21, except one (week 11) (Fig. 2). When the Early1pt method omitted, there were no significant differences across the remaining three methods for the weekly calculations. There was one clinically higher value for the Early1pt compared to the daily method with an APD of 16% at week 3. The differences between the Average2pt and Exp2pt weekly results did not exceed 0.2%.

Effect of start time and calculation methods to 28 days

The box plots of WGV to 28 days showed only minimal skew (Figure S1) and no violation of the normality assumption for the statistical tests. Most of the WGV calculation methods had one high outlier, which on examination was an infant who likely had some fluid retention on day 28 as this infant's weight was lower for a few days following. We did not remove the outlier since this pattern is not an unusual preterm infant weight gain pattern. The box plots for the time of birthweight regain to 28 days had more outliers than those that began at the other times.

Across the various start times (beginning at birth, nadir, or birthweight regain) to 28 days, average WGV ranged from 10.1 to 21.8 g/kg/day, an APD of 73% (Table 3). The differences across the time frames and across the calculation methods were statistically and clinically significant. All of the Early1pt method WGV estimates and those that began when the infants had regained their birthweight were all statistically significantly greater than the others, and greater than our a priori defined clinical significance difference of 10%. Early1pt method gave inflated values relative to the other methods, up to 22 g/kg/day (APD: 15–37%).

All of the estimations that began at birth and included the postnatal weight loss phase were statistically significantly lower, and by more than our a priori defined clinical significance difference of 10%.

After excluding the Early1pt method, the largest difference in WGV was between starting at regain versus day-3 for the Daily method (42%). The day-3 WGV estimates were lower than the nadir for all three WGV calculations by 6 to 21%. The WGV estimates beginning at the day birthweight was regained gave clinical significantly higher estimates (APD: 10–25%) compared to beginning at the nadir.

Once the Early1pt method, beginning at birth, beginning at weight regained and beginning at day 3 were excluded, the WGV estimates ranged from 14.6 to 17.1 g/kg/day, an APD of 18%. The most similar WGV estimates (15.5 to 15.8 g/kg/day, APD of 2%) were obtained across the methods for the calculations beginning between the nadir and 7-day.

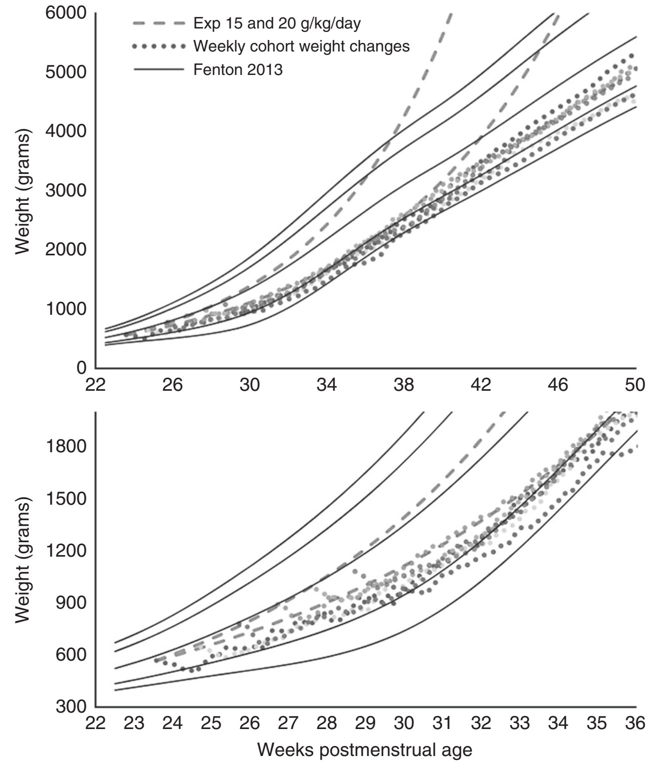

Fig. 1 Patterns of median weight measurements for the infants born at 23–29 weeks gestation (dotted curves) to 50 weeks postmenstrual age (upper panel) and enlarged to 36 weeks (lower panel). Also shown are the median, 3rd, 10th, 90th, and 97th centiles from the girl–boy average Fenton 2013 chart (black curves), and the exponential curves for growth rates of 15 and 20 g/kg/d beginning at 23 weeks (dashed curves)

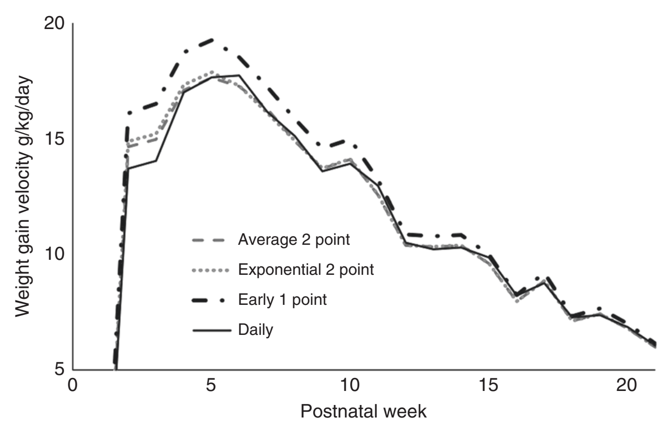

Fig. 2 Weekly growth velocity averages calculated four ways for < 30 weeks 103 weight-appropriate-for-gestational-age preterm infants

DISCUSSION

This study demonstrates that the variation in WGV calculations used in preterm infants are large enough to create difficulty comparing WGV results between studies, to make meta-analyses unreliable and also create problems for the implementation of WGV guidelines in clinical care.[1,2,9] The choices of calculation

Table 3. Weight gain velocity calculated four ways for the first 28 days of life for 103 < 30 week preterm infants with weight appropriate for gestational age, with a focus on the effect of including or excluding the postnatal weight loss transition)[a,b]

	Growth calculation (g/kg/d, mean ± SD)				*P*-values across methods	
Time frame	Daily	Average 2-point	Exponential 2-point	Early 1-Point	All 4 groups	Without 1pt-Early
Birth to 28 days	10.2 ± 3.4	10.1 ± 3.3	10.2 ± 3.4	12.0 ± 4.6	<0.0001	0.002[b]
Nadir to 28 days	14.6 ± 3.8	16.8 ± 3.9	17.1 ± 4.0	21.2 ± 5.9	<0.0001	<0.0001
Regain to 28 days	18.8 ± 5.8	18.6 ± 6.3	18.5 ± 6.0	21.8 ± 7.7	<0.0001	0.38[b]
3 to 28 days	12.4 ± 3.8	13.7 ± 3.8	13.9 ± 3.9	16.9 ± 5.6	<0.0001	<0.0001
7 to 28 days	15.5 ± 4.3	15.6 ± 4.3	15.8 ± 4.4	19.0 ± 6.3	<0.0001	0.10[b]
P-values across time frames						
All 5 time frames	<0.0001	<0.0001	<0.0001	<0.0001		
Excluding birth phase	<0.0001	<0.0001	<0.0001	<0.0001		
Nadir vs regain	<0.0001	0.0014[b]	0.003[b]	<0.0001		
Nadir vs day 7	0.005[b]	<0.0001	<0.0001	<0.0001		
Nadir vs day 3	<0.0001	<0.0001	<0.0001	<0.0001		

[a]Difference greater than 10%, considered clinically significant, calculated as percent difference of the average of the two values
[b]Difference was not statistically significantly different; a Bonferroni adjustment reduced the *p*-value to < 0.0012 for statistical significance.

method and the time-interval both influenced the resulting WGV estimates, which provided WGV results for this cohort that ranged from 10 to 22 g/kg/day. To be able to compare studies and to conduct meta-analyses to summarize findings across studies both require that different methods and differences in time-intervals have not introduced differences. The neonatal community requires consistency in the WGV methods used to describe and summarize growth.

Similar to our previous work on theoretical data,[2] this study on actual preterm growth data shows that the Early1pt method gave inflated values, up to 22 g/kg/day (APD: 15–37%). Given the inflations by the Early1pt method, it seems clear that this method should not be used in the research setting.

The median growth patterns showed that overall these infants were growing at approximately fetal rates after their postnatal weight loss (Fig. 1). Given that most expert groups recommend WGV at fetal rates,[10,11] and do not recommend returning to birth centiles, it makes sense to exclude the postnatal weight loss phase from WGV calculations. Since identifying the weight nadir or birthweight regain may be laborious for individual infants in large datasets, we found WGV calculations beginning at 7 days were not clinically significantly (< 10%) different from calculations beginning at the weight nadir for the Average2pt and Exp2pt and Daily methods. In contrast, calculations beginning at 3 days differed from calculations beginning at the nadir by 16–21%, both clinically and statistically significantly different for each calculation method.

Several recent cohort studies have shown that weight loss can be limited to 7–10% during the first 2–4 days allowing a higher WGV during the first weeks of life when enhancing early nutritional supply in very and extremely preterm infants.[7,12–15] Postnatal growth is well described when WGV for the periods that have different WGV expectations are summarized: postnatal weight loss (averages for proportion lost and nadir day), time to regain birthweight,[7,12–14], and WGV is reported separately for time periods that may include from 7 days to 28 days. Using these time periods allow separate discussions and analyses of these different periods that have different WGV expectations.

Changes in z-scores reveal whether a measure is moving away from or toward the 50th percentile. Weight z-scores among this cohort of AGA infants with some morbidities decreased significantly from birth and then increased slightly after 36 weeks (Table 2). Research needs to define what z-score changes require further investigations[16,17] and how to optimize medical care and nutritional support. In 2012, Senterre and Rigo suggested that initial weight z-score decrease in VLBW infants might be limited to 0.6 to 0.8 z-score during the first 3 days of life when an optimized early parenteral nutrition regimen was applied.[12]

Patel et al. advocated for the exponential WGV method on the basis of fit with the daily calculations and the graph of one infant in each of their papers.[18,19] In contrast to their findings, our analyses revealed Average2pt and Exp2pt calculation methods produced similar WGV estimates for each of the time periods with differences that did not exceed 10% in any of the comparisons and that the fit of the average method to the daily WGV was as good and slightly superior to the exponential method for the WGV calculations to 28 days. The superimposed exponential curves showed that preterm infants do not grow exponentially. Exponential curves only increase so do not reflect infants' postnatal weight loss (Fig. 1).

Since the Average2pt and Exp2pt WGV calculations estimates did not differ by more than 10%, both are based on first order-kinetics (the increments increase based on increasing denominators), and because more people may find the Average2pt method easier to calculate at the bedside, we recommend the Average2pt method be used in clinical settings and research summaries.

The strength of this study is that this cohort had frequent pre- and post-discharge anthropometric measurements, therefore this study was not biased by being influenced by the healthiest infants being lost to follow up. However, this study may have had a selection bias, due the exclusion of infants who had > 6 days of missing weight measures, thereby excluding some sicker infants. Being limited to AGA infants, further study is needed to examine whether infants born small for gestational age infants grow differently, as others have noted.[5–8]

For g/kg/day calculations, we recommend the Average 2-point method [(W2 − W1) / ([(W2 + W1)/2] / 1000) / number of days] (*W* = weight expressed in grams) (Table 1), as it may be more easily understood and implemented in clinical settings compared to the exponential method. We also recommend that the postnatal weight loss phase be excluded from WGV calculations. Our findings support beginning WGV calculations at either day of life 7 or at the weight nadir. We recommend that clinical studies of weight gain to 28 days' report weight nadir and weight at day 7 and 28 to allow adequate comparison and translation of findings in clinical practice.

ADDITIONAL INFORMATION

The online version of this article (https://doi.org/10.1038/s41390-019-0313-z) contains supplementary material, which is available to authorized users.

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