The placenta as modulator of fetal prosperity
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Chapter 3:

Birth weight ratio is a valuable clinical and research tool for fetal growth restriction

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Submitted
Chapter 3

Abstract

Background: Accurate assessment of fetal growth is a principal tool in antenatal care and individual results are usually compared to gestational age-specific centile curves. Reports of obstetrical outcomes in research populations generally use absolute birth weights, and secondarily dichotomize birth weights according to the 10th centile for gestational age. Use of dichotomized data at the extremes discards important information.

Objectives: We coin the term 'Birth Weight Ratio', as the ratio of observed birth weight divided by the mean birth weight of the population-specific reference growth curve

Methods: To demonstrate the advantages of the Birth Weight Ratio, we explored the data from a recent randomized trial in a patient group with early preterm hypertensive complications of pregnancy. The functionality of the Birth Weight Ratio was explored in this patient group.

Results: At delivery women had a median gestational age of 31\(\frac{2}{7}\) weeks (range 26\(\frac{1}{7}\) - 38\(\frac{3}{7}\)). The practical advantages were 1. improved classification of growth restriction as the scale is continuous and not dichotomized. 198 (92%) of infants had a birth weight below the 10th centile. If necessary, tailored dichotomization remains possible; 2. less influence by outliers in the reference curve, especially at lower gestational ages; the difference between Birth Weight Ratios calculated by two different charts is smaller than the differences between centile scores, and less dependent of weight. This shows that the Birth Weight Ratio is more suitable for international comparison of studies on fetal growth restriction.

Conclusion: We advocate to give Birth Weight Ratio a priority position to complement gestational age and absolute birth weights as predictors in reports on obstetric research populations.
Introduction

Gestational age and fetal growth restriction at birth are important determinants for perinatal mortality and morbidity. Accurate assessment of fetal growth in relationship with gestational age is therefore a principal tool in antenatal care. Results are usually compared to centile curves, which are calculated from cross-sectionally acquired data of newborns and dichotomized according to the 10th centile for gestational age. We coin the term ‘Birth Weight Ratio’ as the ratio of observed birth weight divided by the mean birth weight of the population-specific reference growth curve. Values above 1 indicate ‘larger for gestational age than average’ and values below 1 indicate ‘smaller for gestational age than average’. We argue it complements birth weight and gestational age in clinical practice, and can validly replace dichotomization by centile score or another alternative, standard deviation score. We would like to discuss three theoretical arguments

I. No data reduction
Use of the Birth Weight Ratio transforms data into another continuous variable, as opposed to ordinal classes when a percentile is used for classification. This has the advantage that the original value can always be deduced from the transformed value without loss of information, which is not possible when ordinal classes are used. Although, by use of a z-score, percentiles might be used as a semi-continuous parameter, it is customary to dichotomize by the 10th centile, or alternatively the 5th or 2.3rd centile. Dichotomization can be a valuable simplification, despite the fact that there are no specific cut-offs that delineate normal from abnormal growth. However, in tertiary care centers, the 10th centile of birth weight as a threshold classifies a majority of premature deliveries with fetal growth restriction. Thus, in groups at the extremes (e.g. severe fetal growth restriction) important information is lost.

II. Minimized disturbing influence from small sample size (or outliers in reference curves)
The Birth Weight Ratio makes use of the mean of a population reference curve. Many population-specific curves have been constructed from cross-sectional data. In a statistically normal distribution (even if skewed, as birth weights are), the numbers of observations are largest at the mean and outliers have little influence on the mean. This applies especially to low gestational age groups, where the number of cases in most charts is small, and lower or higher centile limits are therefore prone to bias. For these reasons, when relating an individual observation to a reference curve, comparisons using the mean are more reliable.
Chapter 3

III. Superior options for statistical analysis
In contrast to weight centiles, the Birth Weight Ratio is expressed on a continuous and linear scale. This allows more powerful statistical analysis. The interpretation of absolute birth weights is gestational age-specific as 1,100 grams may be ‘normal’ for 28 weeks but ‘abnormal’ for 30 weeks, ‘significantly abnormal’ for 32 weeks and ‘very abnormal’ for 34 weeks. While birth weight in the latter three cases is below the 10th centile, the Birth Weight Ratios are 0.92, 0.72, 0.59 and 0.49 respectively. By use of the Birth Weight Ratio important information is retained for analysis. This provides better opportunity to assess the quantitative correlation and dose-effect dependency between growth restriction and possible causative influences or consequences. Birth Weight Ratio opens opportunities for the uniform interpretation of research results of tertiary care centers in meta-analyses.

Clinical application
To demonstrate the advantages of the Birth Weight Ratio as described above, we explored the data from a recent randomized trial comparing the outcomes of temporizing management with or without plasma volume expansion.2 Women with early preterm hypertensive complications of pregnancy and a singleton pregnancy participated in this study (n=216). At delivery women had a median gestational age of 312/7 weeks (range 261/7 - 383/7). The primary endpoint of the study was an infant neurological test at 40 weeks corrected age.3 This test was performed in 177 of 180 infants alive at term age. It was abnormal in 11 cases. For this study we defined Abnormal Neurological Outcome as the composite measure of death up to one year or abnormal neurological test (n=48). As a secondary composite short term outcome we defined Adverse Neonatal Outcome as death up to one year, major cerebral ultrasound abnormality (intracerebral hemorrhage > grade 2, periventricular leucomalacia > grade 1, or hydrocephalus) or bronchopulmonary dysplasia (additional oxygen after 36 weeks corrected age).4-6 Fifty-five infants were classified as having Adverse Neonatal Outcome. Death until one year had occurred in 38 cases.

In the trial, the customized birth weight chart of Gardosi was used for reference of birth weight. This birth weight chart adjusts for gestational age, infant sex and maternal physiological variables (weight, length, parity and ethnic descent).7 For the analysis presented here this chart was compared to the Kloosterman chart that is commonly used in The Netherlands.8 Statistical analysis was performed with SPSS 12.0.2 (Chicago, U.S.A).
I. No data reduction:
At birth, 198 (92%) of infants had a birth weight below the 10th centile (the 10th centile corresponds to a Birth Weight Ratio of 0.86). Median Birth Weight Ratio of the study population was 0.67 (range 0.29-1.16). Obviously Birth Weight Ratio describes the severity of the fetal growth restriction in the study population more effectively than a 10th centile distribution.

II. Minimized disturbing influence from small sample size or outliers in reference curves:
The mean difference between the 50th centile weight of Kloosterman and Gardosi in the study population was -82 gram (SD 89, range -94 to -70).
In Figure 1A the difference between the 50th centile weight of the Kloosterman and the Gardosi chart is plotted against the average of both measures (Bland-Altman plot). The mean difference for the 10th centile of both charts was -289 (SD 128, range -306 to -272), as depicted in Figure 1B. The 50th centile and the 10th centile weights diverge substantially, with smaller weights in the Kloosterman chart.

In addition, this difference increases with higher birth weight and is larger for the 10th centile weight than for the 50th centile. In contrast, the difference between Birth Weight Ratios calculated by the Kloosterman chart or the Gardosi chart is small (mean 0.030, SD 0.034, range 0.025-0.035), and less dependent of weight, as depicted in Figure 1C. This demonstrates that even if birth weight charts show differences at the extremes the Birth Weight Ratios are more comparable, which makes this measure suitable for international comparison of studies on fetal growth restriction.

III. Superior options for statistical analysis
By use of discriminant analysis we defined the optimum cut-off for the Birth Weight Ratio to predict Abnormal Neurological Outcome and Abnormal Neonatal Outcome. A Birth Weight Ratio below 0.65 proved to be the optimum cut-off to predict Abnormal Neurological Outcome (odds ratio of 2.6 [95% CI 1.3 – 4.9; P = 0.005; sensitivity 60%, specificity 63%]) and Abnormal Neonatal Outcome (odds ratio of 2.6 [95% CI 1.4-4.9; P = 0.003; sensitivity 60%, specificity 63%]). When using the 10th centile of the Gardosi weight chart for prediction the odds ratios were respectively 2.5 (95% CI 0.5 - 11; P = 0.38; sensitivity 96%, specificity 10%) and 2.9 (95% CI 0.7-13; P = 0.16; sensitivity 96%, specificity 10%). This example shows that with a continuous measure, the statistics can be easily adapted to best fit the needs for each specific situation.
Chapter 3
Discussion

The Birth Weight Ratio is not a new parameter, but so far did not receive formal acclaim. To avoid any misunderstanding: Birth Weight Ratio should not replace, but complement gestational age and absolute birth weights as predictors in reports on obstetric research populations. We demonstrated that application of a Birth Weight Ratio allows for better data description, less dependency on the type of birth weight chart and more appropriate statistics than any centile threshold.

Although dichotomisation in itself may be valuable, we believe, along with other authors, there is a need for a continuous measure of the quantity of difference between observed weight and the mean or median for gestational age. Based on statistical presumption the use of multiples of the standard deviation or a semi-continuous percentile distribution might be preferred. However, in clinical practice these measures are scarcely used, probably because they require complex tables. The advantage of the Birth Weight Ratio is that it is easy to implement and that it allows simple statistics due to its linear nature. The Birth Weight Ratio may also be a valuable tool in counseling parents in clinical practice: “Your baby weighs about 75% of what is average for its gestational age” may better convey the message to parents than “Your baby is more than 2.3 standard deviations from what is average for its gestational age” or “… below the 1st centile of our reference chart”.

Conclusion

We think sufficient arguments exist to give Birth Weight Ratio a priority position: it improves comparability, it is reliable, it is easy to understand, easy to use, and provides additional insight. In our opinion, editors of medical journals should encourage that reports on high-risk perinatal populations contain the Birth Weight Ratio.

Figure 1, opposite: Agreement of different Birth Weight measures

1A: Bland-Altman plot of agreement between the 50th centile Kloosterman birth weight chart and the 50th centile birth weight from the Gardosi chart in the study population.
1B: Bland-Altman plot of agreement between 10th centile birth weight from the Kloosterman chart with the 10th centile birth weight from the Gardosi chart in the study population.
1C: Bland-Altman plot of agreement between Birth Weight Ratio calculated from the Kloosterman chart with Birth Weight Ratio calculated from the Gardosi chart in the study population.
Chapter 3

Reference List