Original Article

Formulae Based on Biomathematics to Estimate the Standard Value of Fetal Growth of Japanese

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We devised biomathematics-based formulae to estimate the standard values of fetal growth of Japanese after 22 weeks' gestation. The growth rates of bi-parietal diameter (BPD), abdominal circumference (AC), femur length (FL), and estimated fetal body weight (EFBW) at the time of gestation were assumed to be proportional to the product of the value at the time and the rest value of an unknown maximum value, respectively. The EFBW was also assumed to follow a multiple logistic function of BPD, AC and FL to fit the standard values of Japanese fetuses published by the Japan Society of Ultrasonics in Medicine. The Mann-Whitney test was used for statistical analysis. The values as a function of gestational day, t, were as follows:
$BPD(t) = 99.6/(1 + \exp(2.725 - 0.01837^*t))$ (mm); $AC(t) = 39.7/(1 + \exp(2.454 - 0.01379^*t))$ (cm); $FL(t) = 79.6/(1 + \exp(2.851 - 0.01710^*t))$ (mm); $EFBW(t) = 8045.1/(1 + \exp(6.028 - 0.06582^*BPD(t) - 0.1469^*AC(t) + 0.07377^*FL(t)))$ (g). EFBW as a function of BPD, AC and FL was as follows: $EFBW = 8045.1/(1 + \exp(4.747 + 0.02584^*BPD + 0.1010^*AC - 0.1416^*FL))$ (g). When the BPD, AC and FL were at -2 standard deviation (SD), $-1SD$, mean and $+2SD$, the EFBW values calculated by the formula were statistically closer to the standard values than conventional formulas with p-values of 4.871×10^{-7}, 4.228×10^{-7}, 9.777×10^{-7} and 0.028, respectively. The formulae based on biomathematics might be useful to estimate the fetal growth standard values.

Key words: fetal growth, formulae, biomathematics, Japanese, ultrasound

The Japan Society of Ultrasonics in Medicine (JSUM) published standard values of ultrasonic measurements of Japanese fetuses in 2003 [1]. The published regression formulae for the standard values of bi-parietal diameter (BPD), abdominal circumference (AC), femur length (FL), and estimated fetal body weight (EFBW) have been widely used in the practice of medicine. The regression formulae are cubic functions of time, but the biological or biomathematical reasons behind those functions remain unclear. When the gestational days beyond the domain of definition are applied to the published formulae, the EFBW can be less than zero. This means that the formulae do not explain the biological phenomena but merely show the regression.

We believe that phenomena in nature should be described by mathematics as much as possible. The phenomena in medicine should thus be described by mathematical formulae such as differential equations

that explain the phenomena by themselves, if possible.

The EFBW is a function of the BPD, AC and FL. The EFBW of the published formulae are smaller than the average after 26 weeks of gestation, at which time the BPD, AC and FL are simultaneously larger than the averages, for example +0.1 standard deviation (SD), respectively. This strange contradiction of the published formulae might cause confusion in clinical practice.

To resolve these problems, we created new formulae based on biomathematics to fit the published standard values of the BPD, AC, FL and EFBW. The EFBW formula will never show negative numbers. The EFBW values are greater than the average when the BPD, AC and FL values are simultaneously greater than averages. These formulae were found to be more precise in their predictions and would be able to reduce errors in practical use.

Materials and Methods

The standard values of ultrasonic measurements in Japanese fetuses after 22 weeks of gestation published by the JSUM were used [1-4]. We assumed that the growth rates of the BPD, AC, FL and EFBW on a particular gestational day were proportional to the product of the value at the time and the rest value of an unknown maximum value, respectively. The following differential equation was then created.

$$\frac{dx_i(t)}{dt} = K_i x_i(t)(M_i - x_i(t)),$$

where $i = \{1, \ldots, 4\}$, $\{x_1, x_2, x_3, x_4\} = \{BPD, AC, FL, EFBW\}$, K is the rate constant, M is the maximum value constant, and t is the gestational day. The equation was solved, resulting in a logistic function, and the constants were identified to fit the standard values by using an original program.

We then speculated that the EFBW could be a function of the BPD, AC and FL, as it has often been. Therefore, the EFBW formula could be a multivariate logistic function of the BPD, AC and FL. We hypothesized that when the BPD, AC and FL were the standard values, the EFBW would be closer to the standard value of EFBW. The standard data at −2SD, −1SD, mean, +1SD and +2SD of each number of gestational weeks, all of which follow a normal distribution, are available [1-4]. We weighted the data of ±2SD, ±1SD and mean as 54 : 242 : 399, respectively, which are the integer

ratios of values of the normal distribution probability density function at 2, 1 and 0. As such, the solved formulae would be able to statistically fit the mean and both ±2SD and ±1SD. We used the Mann-Whitney test to compare the formulae with the published formulae.

Results

The formulae of BPD, AC, FL and EFBW as a function of gestational day and the formula of EFBW as a function of BPD, AC and FL are as follows. Units follow the published standard values of ultrasonic measurements in JSUM 2003 [1].

$$BPD(t) = \frac{99.6}{1 + e^{2.725 - 0.001837t}} \text{ (mm)} \ldots \quad (1)$$

$$AC(t) = \frac{39.7}{1 + e^{2.454 - 0.01379t}} \text{ (cm)} \ldots \quad (2)$$

$$FL(t) = \frac{79.6}{1 + e^{2.851 - 0.01710t}} \text{ (mm)} \ldots \quad (3)$$

$$EFBW(t) = \frac{8045.1}{1 + e^{6.028 - 0.06582*BPD(t) - 0.1469*AC(t) + 0.7377*FL(t)}} \text{ (g)} \ldots \quad (4)$$

$$EFBW(BPD, AC, FL) = \frac{8045.1}{1 + e^{4.747 + 0.02584*BPD + 0.1010*AC - 0.1416*FL}} \text{ (g)} \ldots \quad (5)$$

where e is Napier's constant, and t is the gestational day.

The growth curves of the mean in this study and the calculated differences from the actual data are shown in Fig. 1. The AC formula in this study was better than the JSUM's AC formula, whereas the rest of the formulae are not significantly different from those published by the JSUM (Table 1).

The calculated data at ±2SD, ±1SD and the mean in this study and those issued by the JSUM are compared for BPD, AC and FL, respectively, in Fig. 2. The formulae created in this study showed better prediction to the actual data, especially at −2SD, −1SD, the mean and +2SD ($p = 4.871 \times 10^{-7}$, 4.228×10^{-7}, 9.777×10^{-7} and 0.0284, respectively) (Table 2).

Discussion

We obtained a new formula for EFBW using the BPD, AC and FL as well as the formulae of BPD, AC, FL and EFBW as a function of time. This formula for EFBW based on biomathematics shows significantly
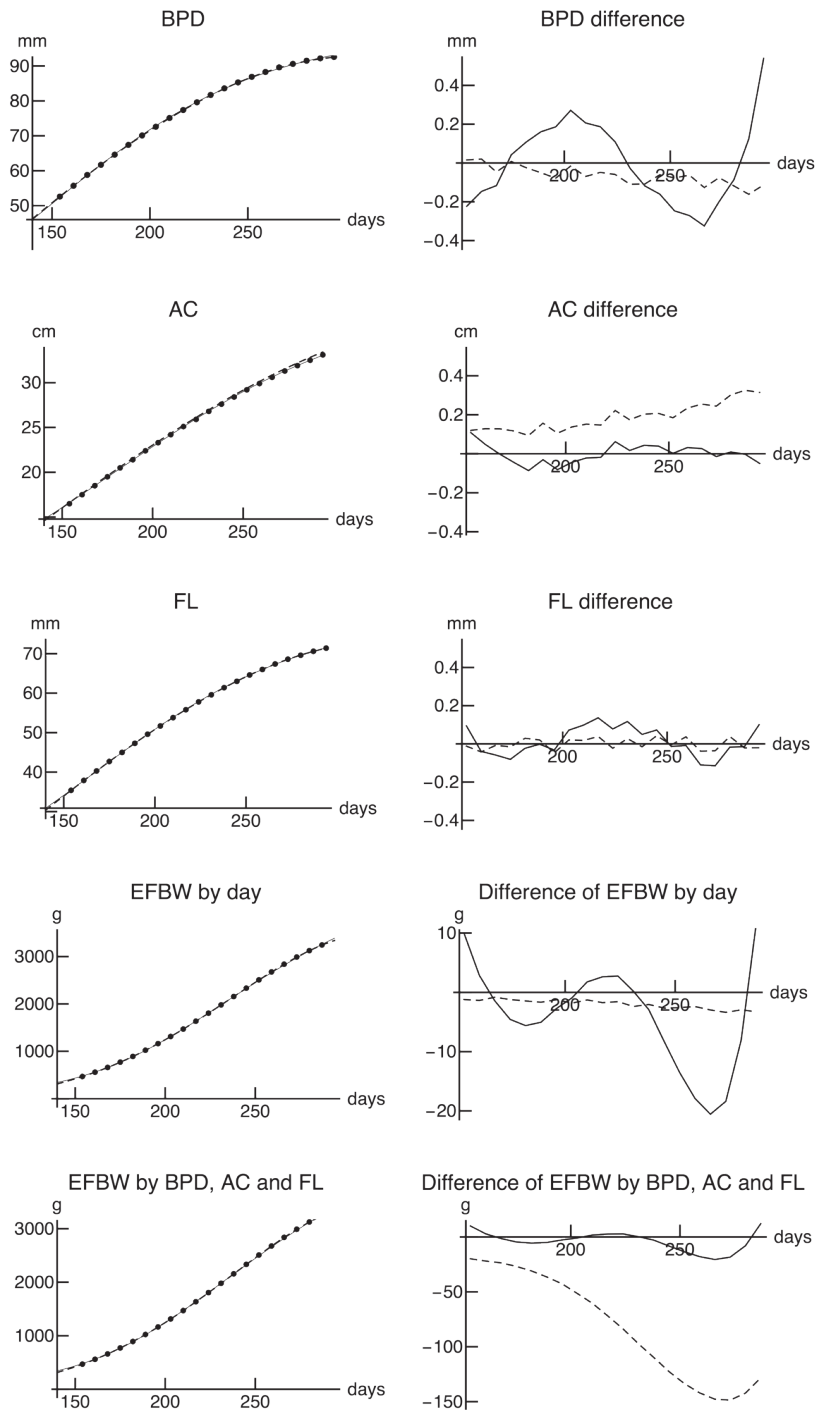
BPD

BPD difference

AC

AC difference

FL

FL difference

EFBW by day

Difference of EFBW by day

EFBW by BPD, AC and FL

Difference of EFBW by BPD, AC and FL

Fig. 1   Comparison of mean data between our new formulae and the current (JSUM) formulae. Left panel: The growth curve in this study, the growth curve in the JSUM publications [1, 5–8], and the actual standard values of BPD, AC and FL are represented by the solid line, dashed line and scattered points, respectively. Note that the solid and dashed lines are very similar. Right panel: The differences between the estimated and actual values. AC, abdominal circumference; BPD, biparietal diameter; FL, femur length; EFBW, estimated fetal body weight.

better prediction for the actual data at the mean, −1SD and ±2SD compared to JSUM 2003 (shown in Table 2). All of the standard data at ±2SD, ±1SD and the mean of each number of gestational weeks are reported to follow a normal distribution [1-4]. The normal distribution function, $f(x) = \dfrac{1}{\sqrt{2\pi}}e^{-\frac{x^2}{2}}$, presents 0.0539/0.2420/0.3989

Table 1   Differences in the actual values and the estimated values of the BPD, AC and FL as a function of number of gestational weeks

	This study	JSUM	p-value
BPD (mm)	0.00062 ± 0.22	-0.065 ± 0.05	0.642
AC (cm)	-0.0005 ± 0.05	0.188 ± 0.07	3.87×10^{-8}
FL (mm)	0.014 ± 0.08	-0.0006 ± 0.03	0.521

AC, abdominal circumference; BPD, biparietal diameter; FL, femur length; JSUM, Japan Society of Ultrasonics in Medicine [1].

Table 2   Comparison of estimated fetal body weight (g) and actual values

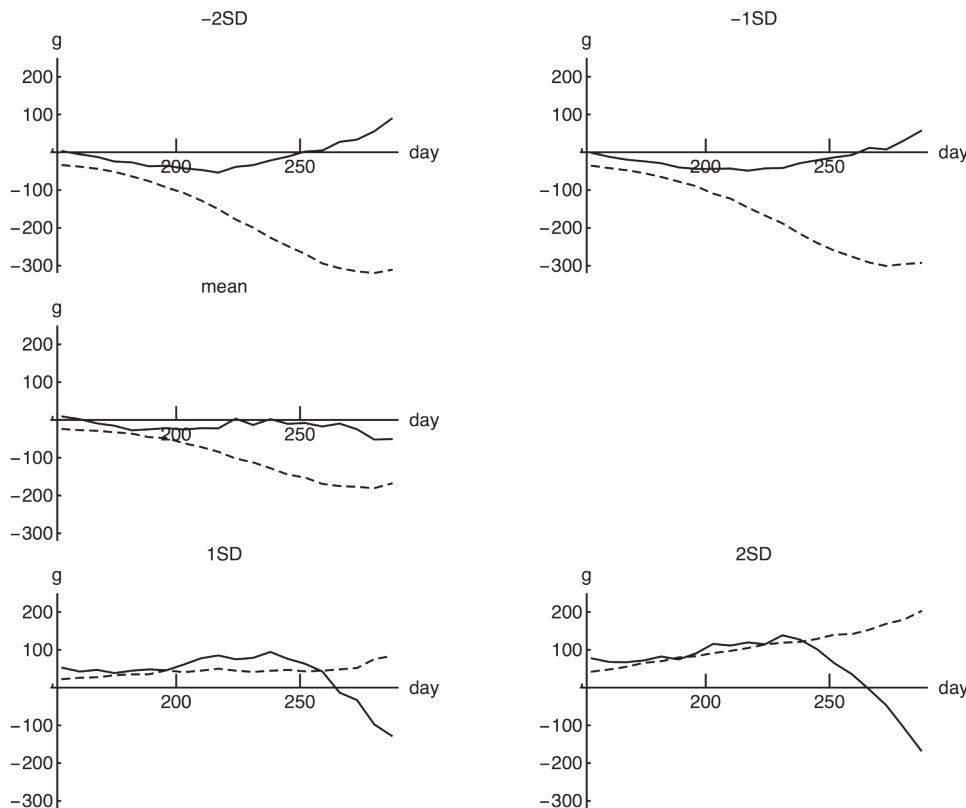|	This study	JSUM	p-value
$-2SD$	-8.66 ± 36.72	-172.59 ± 106.47	4.87×10^{-7}
$-1SD$	-17.63 ± 27.94	-165.90 ± 98.53	4.23×10^{-7}
Mean	-16.84 ± 15.91	-98.41 ± 58.99	9.77×10^{-7}
$+1SD$	35.04 ± 59.11	44.16 ± 14.58	0.214
$+2SD$	56.74 ± 80.08	110.22 ± 44.94	0.028

Fig. 2   Comparison of EFBW for small and large fetuses. The differences between the actual value and the EFBW as a function of BPD, AC and FL when the BPD, AC and FL are all at the mean, ±1SD and ±2SD, respectively. The curve in this study and that of the JSUM [1, 5–8] are represented by the solid line and the dashed line, respectively. The differences calculated by the formula in this study do not increase as much according to the gestational days even in the mean, −1SD and −2SD. After approx. 260 days of gestation, the EFBW in this study is particularly close to the actual value. The formula developed in this study does not show that the smaller the fetus, the much smaller the estimation. It also does not show that the larger the fetus, the much larger the estimation.

when x is $\pm 2 / \pm 1 / 0$, respectively. The ratio of 0.0539/ 0.2420/0.3989 can then be converted to 54/242/399 by using the integer. We weighted those numbers to each standard data before the multivariate logistic functions were obtained. The logistic function in this study can thus cover not only the mean data but also the periph-

eral data such as ±2SD and ±1SD. The formulae we devised in this study therefore seem to show more precise determination.

The new formula does not underestimate the EFBW by much and shows less deviation at −2SD, −1SD, +1SD and +2SD, especially around 260-270 days of

gestation. The formula for the EFBW published by the JSUM has been clinically used in Japan and as such, the formula might not need modification. However, because it is important for clinicians to obtain more precise estimates and to detect extremely small or extremely large fetuses, the formula in this study might provide more useful information for fetal management. For example, when the BPD, AC and FL are at the mean, the EFBW should also be the mean. The EFBW in this study is only −50 g at approx. 280 days of gestation compared with the actual data, whereas the EFBW reported by the JSUM at that date is −160 g (Fig. 2).

With regard to the biomathematics, the formulae obtained by the differential equations are thought to be biologically significant. All of the new formulae for BPD, AC, FL and EFBW described in this study are monotonically increasing functions, although the formulae that are cubic functions of time in the JSUM show decline curves after approx. 300 days of gestation and the EFBW could be less than zero. This means that the JSUM formulae do not explain the biological phenomena by themselves.

We believe that the phenomena in nature should be described by mathematics as much as possible, and we were able to define the mathematical formulae by differential equations that explain the phenomena by themselves. We assumed that the growth rate of the BPD, AC, FL and EFBW on a particular gestational day was proportional to the product of the value at the time and the rest of an unknown maximum value, respectively. We propose that this assumption is likely to be right because the formulae in this study showed a precise fit. Moreover, the formulae were found to be more precise in their prediction and would be able to reduce errors in practical use. The concept that biological phenomena

should be explained by mathematical formulae and confirmed by statistics is likely to be very important for biological scientists seeking to understand more aspects of nature.

In conclusion, our formulae based on biomathematics could be useful to estimate the standard values of fetal growth. The formulae can enable more precise determinations of the estimated fetal body weight, thereby allowing clinicians and investigators to critically examine the importance of biomathematics on predicting fetal growth.

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