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CLINICAL ARTICLE

Chinese weight-correction model for maternal serum markers in Down syndrome prenatal screening

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Abstract

Objective: To determine the best weight-correction model by means of analyzing the relationship between maternal weight and maternal serum markers when screening for Down syndrome in China. *Methods:* Serum levels of α-fetoprotein (AFP) and free β-human chorionic gonadotropin (hCG) were measured in 35,917 Chinese women during the second semester of a normal singleton pregnancy and converted to multiple of median (MoM) values. Using 2 methods of statistical analysis, the all-point method and the median regression method, 4 weight-correction models were then tried, the simple linear, reciprocal, quadratic, and log-linear regression models. *Results:* The median regression method performed better than the all-point method, and the quadratic regression model showed the best fit for both AFP and hCG in the median regression method, with adjusted R^2s of 0.987 and 0.988, respectively. *Conclusion:* The quadratic regression model was found to be the most suitable for Chinese pregnant women.
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1. Introduction

Down syndrome (also called trisomy 21) is the most common chromosomal abnormality, with an incidence of 1 for every 800 to 1000 live births. There is no treatment for this disease, but prenatal screening and diagnosis can warn of its occurrence [1]. Prenatal screening for Down syndrome was introduced in China several years ago, and it is necessary to build a database and a risk-estimation model specific to China.

2. Methods

2.1. Study participants

The records of women with a singleton pregnancy who participated in the second-semester screening program for Down syndrome at Shen Yang Maternal and Child Health Hospital from June 2000 to December 2003 were reviewed. To be

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analyzed, the records had to include all data concerning a carefully monitored pregnancy and a healthy birth. The records of 35,917 Chinese women were analyzed.

2.2. Clinical management

The women who reported for prenatal screening for Down syndrome between the 14th and 20th week of pregnancy were fully aware of the reason for the test. Gestational age was estimated by the last menstrual period if the cycle had been regular, or by ultrasonographic scan. Serum α-fetoprotein (AFP) and free β-human chorionic gonadotropin (hCG) concentrations were measured using Wallac DELFIA hAFP/Free hCGβ Dual kits (DELFIA Xpress; PerkinElmer Life and Analytical Sciences, Inc., Wellesley, MA, USA). Quality control was conducted throughout the 3-part process. Down syndrome affected pregnancy was definitively established by karyotype analysis of the amniocentesis fluid or of the newborns' peripheral blood cells.

The first part (before sampling for screening) included gestational age estimation and a eugenics consultation; the second part (sample collection, preservation, and evaluation) included actual sampling, sample copy preservation, sample examination, and risk calculation the third part (after sampling) included prenatal diagnosis of pregnancies at high risk, surveillance of pregnancy outcome, report on delivery, and Down syndrome confirmation.

2.3. Statistical analysis

The median levels of serum markers at various gestational ages were calculated and all data were converted to multiples of the median value (MoMs) [2,3]. Two methods were used to assess the relationship between MoMs of serum markers levels and maternal body weight. One was the all-point regression method, in which all individually observed data were involved. The other was the weighted median regression method, in which only the weighted median for various weight groups were used. The median MoMs were calculated separately in the 13 maternal weight groups (at 5-kg intervals). These values were then weighted by frequency, and subjected to regression estimation together with the median maternal weight of the corresponding weight group. The relationship between maternal weight and MoM of serum marker levels was analyzed by simple linear, reciprocal, quadratic, and log-linear regression using both the all-point method and the weighted median regression method. The selection of the most suitable model was not only based on the multiple determination coefficients (the R squares or the adjusted R^2s) but also on the effect of the weight correction. Comparisons of standard deviations of the corrected MoMs were carried out between those obtained using the log-linear model of the all-point method and those obtained using the quadratic model of the median regression method. The expected values for AFP and hCG MoMs were calculated according to the appropriate equation. The MoMs were corrected for maternal weight according to the following 2 formulas:

$$\text{AFP}_{\text{corr}} = \text{AFP MoM}_{\text{observed}}/\text{AFP MoM}_{\text{expected}}, \text{ and}$$

$$\text{hCG}_{\text{corr}} = \text{hCG MoM}_{\text{observed}}/\text{hCG MoM}_{\text{expected}},$$

where ($\text{MoM}_{\text{expected}}$ was calculated according to the equation listed in Table 1).

Table 1 Regression equation estimation results

Methods	Regression equation	R^2
Median regression methods		
AFP MoM		
Simple linear	AFP MoM = 1.6011 − 0.0103 × weight	0.949
Reciprocal	AFP MoM = 0.3387 + 38.0288 / weight	0.983
Quadratic	AFP MoM = 2.1475−0.0280 × weight + 0.0001 × weight^2	0.987*
Log-linear	LnAFP MoM = 0.268 − 0.00459 × weight	0.962
hCG MoM		
Simple linear	hCG MoM = 1.7502 − 0.0129 × weight	0.911
Reciprocal	hCG MoM = 0.1515 + 48.6110/weight	0.982
Quadratic	hCG MoM = 2.7354 − 0.0448 × weight + 0.0003 × weight^2	0.988*
Log-linear	LnhCG MoM = 0.333 − 0.005751 × weight	0.937
All-point methods		
AFP MoM		
Simple linear	AFP MoM = 1.713595 − 0.010923 × weight	0.033
Reciprocal	AFP MoM = 0.368268 + 40.491,964 / weight	0.035
Quadratic	AFP MoM = 2.359524 − 0.031812 × weight + 0.000165 × weight^2	0.035*
Log-linear	LnAFP MoM = 0.256495 − 0.004468 × weight	0.043
hCG MoM		
Simple linear	hCG MoM = 2.318608 − 0.016871 × weight	0.014
Reciprocal	hCG MoM = 0.225299 + 63.431436 / weight	0.015
Quadratic	hCG MoM = 3.415168 − 0.052332 × weight + 0.000280 × weight^2	0.015*
Log-linear	LnhCG MoM = 0.331268 − 0.005486 × weight	0.024

Abbreviations: AFP, α-fetoprotein; hCG: free β-human chorionic gonadotropin; MoM, multiple of median.
*When the quadratic term was significant ($P < 0.05$), the adjusted R^2 was listed here instead of the R^2.

After model selection, the difference between uncorrected and corrected data (using the selected model) was compared for every weight group. All statistical analyses were carried out using the statistical software SPSS, version 10.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Maternal weight and serum markers distribution

The mean maternal weight was 58.9 kg, the mean maternal age was 27.0 years (Table 2), and 97.5% of the women were younger than 35 years on the expected delivery date. A negative correlation between maternal weight and maternal

Table 2 Distribution of maternal age and MoMs of serum markers in different weight-groups

Weight group, kg	No. of women	Maternal age, y	GA, wk	Maternal weight, kg		AFP		hCG	
		$\bar{X}\pm$SD	$\bar{X}\pm$SD	$\bar{X}\pm$SD	M	$\bar{X}\pm$SD	M	$\bar{X}\pm$SD	M
≤40	79	26.55±3.83	16.65±1.29	38.92±1.47	40.00	1.24±2.21	1.34	1.34±2.42	1.39
40–45	1040	26.05±3.04	16.96±1.28	43.82±1.28	44.00	1.18±1.52	1.18	1.31±2.15	1.28
45–50	4534	26.33±3.14	17.12±1.33	48.48±1.40	49.00	1.12±1.49	1.12	1.20±2.04	1.15
50–55	8344	26.71±3.30	17.20±1.35	53.23±1.44	53.00	1.05±1.54	1.05	1.10±2.05	1.06
55–60	8831	27.07±3.43	17.29±1.35	58.08±1.46	58.00	1.00±1.52	1.00	1.03±2.03	0.99
60–65	6165	27.39±3.57	17.34±1.35	62.96±1.46	63.00	0.95±1.47	0.95	0.97±1.97	0.93
65–70	3499	27.61±3.80	17.36±1.35	67.90±1.49	68.00	0.91±1.52	0.90	0.91±2.02	0.85
70–75	1859	27.61±3.84	17.37±1.35	72.81±1.47	72.50	0.86±1.53	0.84	0.85±1.98	0.81
75–80	858	27.27±3.90	17.44±1.32	77.85±1.51	78.00	0.81±1.49	0.81	0.83±1.97	0.80
80–85	378	27.71±3.89	17.36±1.34	82.87±1.41	83.00	0.79±1.47	0.79	0.81±2.05	0.79
85–90	183	27.52±3.64	17.42±1.38	87.76±1.45	87.50	0.72±1.52	0.73	0.72±2.07	0.68
90–95	74	27.39±3.91	17.74±1.40	92.91±1.55	93.00	0.74±1.53	0.74	0.67±2.02	0.65
>95	73	27.58±3.95	17.26±1.44	107.03±11.29	104.00	0.86±1.56	0.85	0.78±2.07	0.85
Total	35917	27.01±3.49	17.26±1.35	58.90±8.82	58.00	1.00±1.53	0.99	1.03±2.05	0.99

Abbreviations: AFP, α-fetoprotein; GA, Gestational age; hCG, free β-human chorionic gonadotropin; M, median; MoM, Multiple of median; $\bar{X}$, mean. The $\bar{X}$, SD, and M were the antilog values based on $\log_{10}$ (MoM).

serum markers levels was found ($P<0.05$). The coefficient of correlation was −0.182 for AFP and −0.119 for hCG.

3.2. Regression of maternal weight and serum marker MoMs

The multiple determination coefficients were higher than 75% using the weighted median regression method and lower than 10% using the all-point method. With the weighted median regression method, the quadratic regression model provided the highest adjusted R^2s for both AFP and hCG. Using the all-point method, the log-linear regression model showed higher R^2s. The standard deviation was smaller using the quadratic regression (with the medians method) than the log-linear regression (with the all-point method). Details are showed in Table 3. It seemed that the quadratic model from the median regression method was the most suitable for this Chinese population, and the quadratic regression (with the medians method) was therefore selected as the weight-correction model.

Figs. 1 and 2 show the difference between the regression curves (with the medians method) for the estimated and observed median levels of serum markers. The quadratic regression curve was close to the observed medians for both AFP and hCG, which confirmed the results showed in Table 1.

The medians of the weight-corrected values were close to 1 after correction. The corrections therefore minimize the variations in serum marker levels caused by variations in maternal weight. The distributions of medians of MoMs after weight correction are shown in Table 4.

Table 3 Comparison of the weight-correction results

Method	AFP MoM			hCG MoM		
	Mean	Median	SD	Mean	Median	SD
Without correction	0.995	0.991	1.530	1.029	0.989	2.045
Median regression quadratic	1.000	0.995	0.863	1.004	1.003	1.127
All-point regression log-linear	1.000	1.002	1.199	1.009	0.995	1.360

The mean, median, and standard deviation (SD) are the antilog values based on $\log_{10}$ (MoM).

4. Discussion

Antenatal screening for fetal Down syndrome was introduced in the 1960s among older pregnant women, and was gradually integrated in general practice as several maternal serum markers were found to be associated with fetal Down

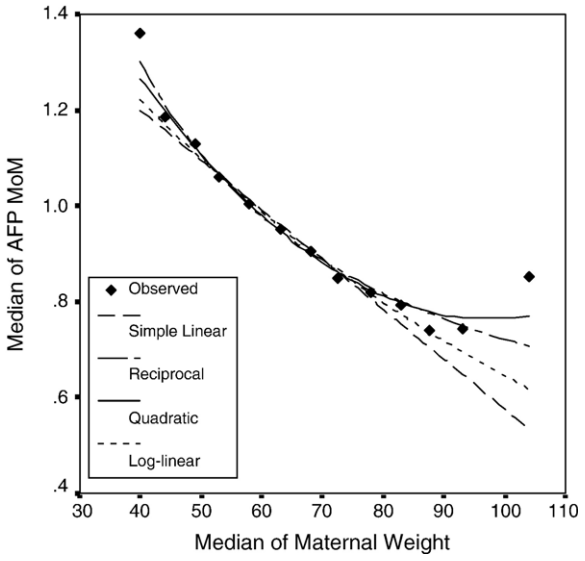

Figure 1 Comparison of different regression equations between maternal weight median and AFP MoM median.

syndrome [4–7]. Multiple marker protocols were then developed to screen for Down syndrome [8–11]. In this study, second-trimester values were selected by means of 2 methods to establish the maternal weight-correction equation.

Wald and associates [12] reported a negative correlation between maternal weight and serum AFP levels, and suggested that the correction according to maternal weight should be done before estimating the risk for Down syndrome. Several models such as the linear, the exponential, and the reciprocal models have been used to correct the effect caused by maternal weight [13–15]. Initially, a log-linear model was constructed to adjust for the effect caused by the maternal weight. Later, an exponential model was found to be better than log-linear model [16]. In 1996, an analysis of data from 47,585 white women concluded that the reciprocal model was better than both the log-linear and exponential models. The reciprocal model has a wide extension, which can fit a maternal weight between 80 and 350 lb [17]. Many researchers have followed this method of adjusting for maternal weight [18–20].

In the present study, the quadratic model rather than the reciprocal model provided the best-fit equation, and the same finding was reported by Jou and associates [21]. The mean maternal weight in their study was 54.9 kg, which was close to the mean maternal weight in this study. In general, Chinese women are much lighter than white women, whether pregnant or not. Since maternal weight varies among populations, the correction formula for maternal weight should be determined for each population. In the present study, AFP and hCG MoMs were compared before and after weight correction to prove that the weight-correction equation was suitable. The corrected MoMs in this study were close to 1.00 and their standard deviations were smaller than those of uncorrected MoMs. This demonstrated that the quadratic correction equation was efficient and suitable for this population. The difference between the quadratic equation and the most-accepted reciprocal equation may be caused by differences in weight distribution or race. Wald and coworkers [22] reported that lighter women had, on average, higher AFP levels than heavier women, and explained this phenomenon by a greater concentration of AFP relative to a smaller blood volume. In the present study, a positive relationship between maternal weight and serum marker levels was found when maternal weight was greater than 95 kg, a finding which may affect the selection of the best weight-correction equation. The data were from women living in the Northern China province of Liaoning, and only 73 women in this population weighed more than 95 kg. More data should be collected among women of high body weight and further studies are needed to establish whether the quadratic model is the best for Chinese pregnant women.

In conclusion, the quadratic model in the weighted median regression method showed a better performance in this population of Chinese pregnant women.

Table 4 Distribution of the median of observed and corrected MoMs grouped by maternal weight

Weight groups, kg	Median of AFP MoM		Median of hCG MoM	
	Observed	Corrected	Observed	Corrected
≤40	1.3435	1.0457	1.3908	1.0034
41–45	1.1756	0.9766	1.2836	1.0152
46–50	1.1186	1.0007	1.1523	0.9865
51–55	1.0496	1.0000	1.0614	0.9905
56–60	0.9955	0.9999	0.9925	1.0071
61–65	0.9452	0.9976	0.9328	1.0194
66–70	0.8961	0.9907	0.8507	0.9999
71–75	0.8407	0.9694	0.8057	1.0131
76–80	0.8120	0.9705	0.7979	1.0472
81–85	0.7864	0.9691	0.7892	1.0595
86–90	0.7309	0.9357	0.6843	0.9356
91–95	0.7382	0.9633	0.6523	0.8884
>95	0.8487	1.1711	0.8491	1.0108
All	0.9911	0.9952	0.9891	1.0034

Abbreviations: AFP, α-fetoprotein; hCG: free β-human chorionic gonadotropin; MoM, multiple of median. $MoM_{corrected} = MoM_{observed}/MoM_{expected}$.

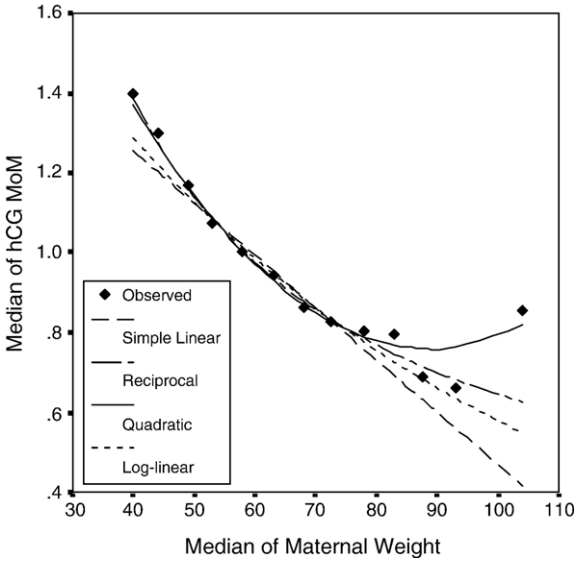

Figure 2 Comparison of different regression equations between median maternal weight and hCG MoM median.

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