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Korean-Specific Parameter Models for Calculating the Risk of Down Syndrome in the Second Trimester of Pregnancy

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The purpose of the current study was to propose a Korean-specific parameter set for calculating the risk of Down syndrome in the second trimester of pregnancy and to determine the screening performances of triple and quadruple tests in Korean women. Using the data on triple or quadruple screening from three hospitals in Korea during 7 yr, we re-converted the concentrations of four serum markers to multiple of median values according to gestational age and maternal weight. After re-calculating the risk of Down syndrome in each pregnancy by multiplying maternal age-specific risk by the likelihood ratio values for the serum markers, screening performances and optimal cut-off values of triple and quadruple tests were analyzed. Among 16,077 pregnancies, 23 cases had Down syndrome (1.4/1,000 deliveries). Compared to the previous program, the tests with new parameters had improved screening performance. The triple and quadruple tests had detection rates of 65.2% and 72.7%, respectively, at a false-positive rate of 5%. The optimal cut-off value for the quadruple and triple tests was 1:250. We have presented a Korean-specific parameter set for Down syndrome screening. The proposed screening test using this parameter set may improve the performance of Down syndrome screening for Korean women.

Key Words: Down Syndrome; Korean-Specific; Second Trimester Screening; Triple Test; Quadruple Test; Serum Marker

INTRODUCTION

Down syndrome is the most common chromosomal anomaly, with an incidence at birth of 1 per 800-1,000 (1, 2). Amniocentesis or chorionic villous sampling for prenatal chromosomal analysis is difficult to be performed in all patients because of the risk of fetal loss and the cost (3). Accordingly, prenatal screening to identify pregnancies at increased risks for Down syndrome is very important.

Since Cuckle et al. (4) reported that a low level of serum α- fetoprotein (AFP) is a high-risk marker for Down syndrome in 1984, several maternal serum markers have been developed. Measuring maternal serum levels of AFP, total human chorionic gonadotrophin (hCG), and unconjugated estriol (uE3) is known as triple screening (5, 6). The quadruple test, which adds inhibin A, was introduced in the early 2000s (7, 8). To calculate the risk of Down syndrome using serum markers, commercially available software programs are used in practice. Because variances are observed between software programs, it is effective that each country has a software program to apply variances and covariances of serum markers for its own population to achieve accurate screening.

In Korea, the triple and quadruple tests have been used widely among pregnant women since December 2004 and October 2009 under the support of National Health Insurance, respectively. However, the accuracy of Down syndrome screening tests is questionable in Korea, because the software programs in use were mainly based on dataset compiled from Western women. In addition, little information is available on the performance of these screening tests for Korean women. Few reports have analyzed the performance of triple screening in Korea, but the sample sizes were small (9, 10).

Recently, ethnic differences in serum marker levels have been reported (11-13), and the maternal age-related risk for Down syndrome was also reported to be different among races (14). Therefore, it is requested to establish screening tests specific for each race or region (15). Accordingly, in this study, we determined the covariances of serum markers for triple and quadruple screening tests in a Korean population, and re-calculated the risk of Down syndrome using newly determined values. Then, we compared the performances with those by software currently in use. This study introduces a dataset for Down syndrome serum screening and cut-off values specific for pregnant Korean women.

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MATERIALS AND METHODS

Study participants

We analyzed the medical records of all pregnant Korean women who underwent triple or quadruple screening test between 14 and 21 weeks gestation at Seoul St. Mary's Hospital and Yeouido St. Mary's Hospital (2002-2009), and Cheongwha Women's Medical Center (2005-2009). A total of 17,890 pregnant women had second trimester screening tests; 1,813 pregnant women who had no records on fetal outcomes were excluded and 16,077 pregnant women were analyzed. Based on the records of screening tests, we determined the serum levels of AFP, hCG, uE3, and inhibin A, and the expected risk of Down syndrome. For those pregnant women who underwent amniocenteses, we checked the karyotype results, and for the pregnant women who did not undergo amniocenteses, we investigated the presence of fetal Down syndrome using neonatal charts on the date of birth and 1 month after birth.

Screening performances of triple and quadruple tests based on the HIT program

Gestational age (GA) was estimated by the menstrual history if regular or by ultrasonographic scan. Maternal age referred to age at the time of expected delivery date. Maternal serum levels of AFP, hCG, uE3, and inhibin A were determined using the Unicel™ Dxl 800 Access Immunoassay System with reagents (Beckman Coulter®, Inc., Fullerton, CA, USA). The screening performances of the triple or quadruple tests based on the HIT program (Hamchoon Inc., Seoul, Korea) with a cut-off value of 1:270 were calculated.

Down syndrome risk assessment using newly established parameters of serum markers

To correct the variable changes in serum marker concentrations according to gestational age, the concentrations were converted to multiple of the median (MoM) values for the relevant gestational ages. To provide reliable medians, regression analysis of each serum marker on gestational age among unaffected pregnancies was performed using the median concentration of each serum marker and median gestation (in days) for pregnancies at each completed week of pregnancy, weighted for the number of women at each week. The MoMs were calculated separately in each hospital according to the median values obtained from following regression equations: AFP (ng/mL) = $10^{(0.7569 + 0.0078 * GA)}$; hCG (IU/mL) = $10^{(6.5772 - 0.0733 * GA + 0.0003 * GA * GA)}$; uE3 (ng/mL) = -4.4196 + 0.0499 * GA; Inhibin A (pg/mL) = $10^{(0.7569 + 0.0078 * GA)}$.

And then, all of the MoMs for the four serum markers were corrected for maternal weight using the weighted median regression method. The median MoMs were calculated separately in the 14 maternal weight groups (at 5-kg intervals). The values were then weighted by frequency, and subjected to regression estimation together with the median maternal weight of the corresponding weight group. Among simple linear, quadratic, log-linear, and log-quadratic regression models, the most suitable model was based on the multiple determination coeffecients (the R square). The weight-adjusted MoMs were calculated according to the following formula: AFP_{corr} = $AFP\ MoM_{observed}/AFP\ MoM_{expected}$, where $MoM_{expected}$ was calculated according to the selected regressed equation: AFP (MoMs) = 2.2856 - 0.0328 * kg + 0.0002 * kg * kg; hCG (MoMs) = $10^{(0.2636 - 0.0047 * kg)}$; uE3 (MoMs) = $10^{(0.1848 - 0.0043 * kg + 0.00002 * kg * kg)}$;. inhibin A (MoMs) = $10^{(0.3085 - 0.0078 * kg + 0.00004 * kg * kg)}$.

All weight-corrected MoM values were converted to log-equivalents to obtain the distribution parameters. Goodness-of-fit to log-Gaussian distribution for the marker values was judged by inspection of the log-probability plot for unaffected pregnancies and the Kolmogorov-Smirnov test for affected pregnancies. Upper and lower truncation limits were set within which the available data adequately fitted the Gaussian model judged by inspection of the log-probability plot. Values outside those limits were given MoM values at the appropriate limit. The truncation limits for markers were 0.5-2.0 MoM for AFP, 0.3-2.7 MoM for uE3, 0.5-1.7 MoM for hCG, and 0.5-2.1 MoM for inhibin A.

The mean and standard deviations for each marker in unaffected and affected pregnancies were calculated by using the $\log_{10}$ of the median as the mean. The risk of Down syndrome was assessed by a commonly used risk algorithm. The likelihood ratio (LR) obtained with each marker was the height of the Gaussian distribution for the Down syndrome pregnancies divided by the height of the Gaussian distribution for the unaffected pregnancies at the particular value of the variables concerned. Age-specific risk was derived from the previous report of maternal age-specific rates of Down syndrome in Korean pregnant women (13).

The case-specific risks of Down syndrome in triple and quadruple tests were estimated using the following equations: risk with triple screening = risk age * LR (AFP) * LR (HCG) * LR (uE3); risk with quadruple screening = risk age × LR (AFP) * LR (HCG) * LR (uE3) * LR (inhibin A).

Statistical analysis

We compared the incidence of Down syndrome between pregnancies in which the maternal age was < 35 yr and pregnancies in which the maternal age was ≥ 35 yr by Student's t-test. The median concentrations and MoMs of the serum markers were compared with published values for Caucasian women for the relevant gestational age by calculating the ratio. The MoM values of serum markers between unaffected and Down syndrome pregnancies were compared using Student's t-test.

Detection and false-positive rates for Down syndrome were re-calculated for all pregnancies. In particular, to determine the optimal cut-off value, we constructed the area under the receiver

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operating characteristic (AUROC) curve. A P value < 0.05 was considered statistically significant. All statistical analyses were carried out using SPSS (version 12.0; SPSS Inc., Chicago, IL, USA).

Ethics statement

The study was approved by the institutional review board of the College of Medicine of the Catholic University of Korea (KC10RES10193, SC11RIM10074). The board waived informed consent from the subject patients. It was conducted in accordance with the Declaration of Helsinki.

Table 1. Demographic characteristics of all pregnancies and pregnancies complicated by Down syndrome

Characteristics	Total pregnancies (N = 16,077)	Down syndrome pregnancies (N = 23)
Maternal age at expected date of delivery (yr)		
< 35	13,499	10
≥ 35	2,578	13
Second trimester screening test*		
Triple test (Women with positive screening)	8,085 (595)	12 (8)
Quadruple test (Women with positive screening)	7,992 (632)	11 (9)
Pregnancies with type 1 diabetics	7	0
Gestational age of fetus at screening test	116.7 ± 7.4 days	115.4 ± 8.2 days
14-17 week	14,395	20
19-21 week	1,682	3
Maternal weight	57.2 ± 8.5 kg	59.0 ± 10.4 kg

All data are expressed Number of pregnancies or mean ± SD. *Screening analysis using HIT program (Hamchoon Inc., Seoul, Korea) at a cutoff value of 1:270.

RESULTS

Demographic characteristics

Among the 16,077 pregnancies, Down syndrome occurred in 23 cases (1.4/1,000 newborns). The demographic characteristics of the pregnancies included in this study are summarized in Table 1. The mean maternal age was 31.1 ± 3.5 yr, and the mean maternal weight was 57.2 ± 8.5 kg. Among the gravidas > 35 yr of age, the prevalence of Down syndrome was 5.0 per 1,000 newborns, which was significantly higher than the 0.7 per 1,000 newborns among the gravidas < 35 yr of age (P = 0.002).

Triple and quadruple screening tests were performed on 8,805 and 7,992 pregnancies, respectively. Among the 23 fetuses with Down syndrome, 17 had positive triple or quadruple screening tests; 4 and 2 fetuses had negative triple and quadruple screening tests using the HIT program, respectively.

The serum concentrations and MoMs of four serum markers for Down syndrome and unaffected pregnancies

When the median values of the serum markers at each gestational age were compared with the published values for Caucasian women (16), the median values of all the serum markers were higher in Korean women than Caucasian women. The range of ratios was highest for inhibin A (range, 1.5-1.9), followed by uE3, AFP, and hCG (Table 2).

Table 2. Comparison of median maternal serum concentrations of AFP, hCG, uE3 and inhibin A between Korean and Caucasian women with unaffected pregnancies

GA (wk)	AFP (ng /mL)			hCG (IU/mL)			uE3 (ng/mL)			Inhibin A (pg/mL)		
	Korean	Caucasian*	Ratio†	Korean	Caucasian*	Ratio†	Korean	Caucasian*	Ratio†	Korean	Caucasian*	Ratio†
15	39.5	33.3	1.2	46.8	42.4	1.1	0.98	0.73	1.4	207	112	1.9
16	44.7	37.6	1.2	36.3	34.1	1.1	1.33	0.92	1.4	184	108	1.7
17	50.7	42.5	1.2	29.8	28.3	1.1	1.68	1.15	1.5	171	104	1.7
18	57.4	48.0	1.2	26.0	24.1	1.1	2.03	1.43	1.4	167	105	1.6
19	65.1	54.3	1.2	24.1	21.2	1.1	2.38	1.79	1.3	170	118	1.5
20	73.8	61.3	1.2	23.6	19.1	1.2	2.73	2.24	1.2	181	124	1.5

All data are expressed as median values. *Data for Caucasian women were reported by MacRae et al. (15); †Ratio of the serum markers' medians calculated in this study to those in a published study with Caucasian women for the relevant gestational age. GA, gestational age; wk, week; AFP, α-fetoprotein; hCG, human chorionic gonadotrophin; uE3, unconjugated estriol.

Table 3. Statistical variables of log transformed and untransformed Gaussian distributions of each serum marker, expressed in multiple of the median (MoM) values in Down syndrome and unaffected pregnancies

Variables	Unaffected pregnancies				Down syndrome pregnancies			
	AFP	hCG	uE3	Inhibin A	AFP	hCG	uE3	Inhibin A
Mean*	1.05	1.09	1.01	1.08	0.82	2.13	0.73	2.65
Median	1.00	1.00	1.00	1.00	0.82 (0.74)‡	1.80 (2.05)‡	0.74 (0.70)‡	2.54 (2.54)‡
Log_{10} means†	0.00	0.00	0.00	0.00	-0.09	0.26	-0.13	0.41
Log_{10} S.D.	0.15	0.22	0.16	0.20	0.16	0.20	0.25	0.12

*Comparison between unaffected pregnancies and Down syndrome pregnancies; P = 0.012, 0.001, 0.001, and < 0.001, by Student t test for AFP, hCG, uE3, and inhibin A respectively; †The log_{10} means were estimated from the medians; ‡Values in parentheses were reported by Wald et al. (16). AFP, α-fetoprotein; hCG, human chorionic gonadotrophin; uE3, unconjugated Estriol.

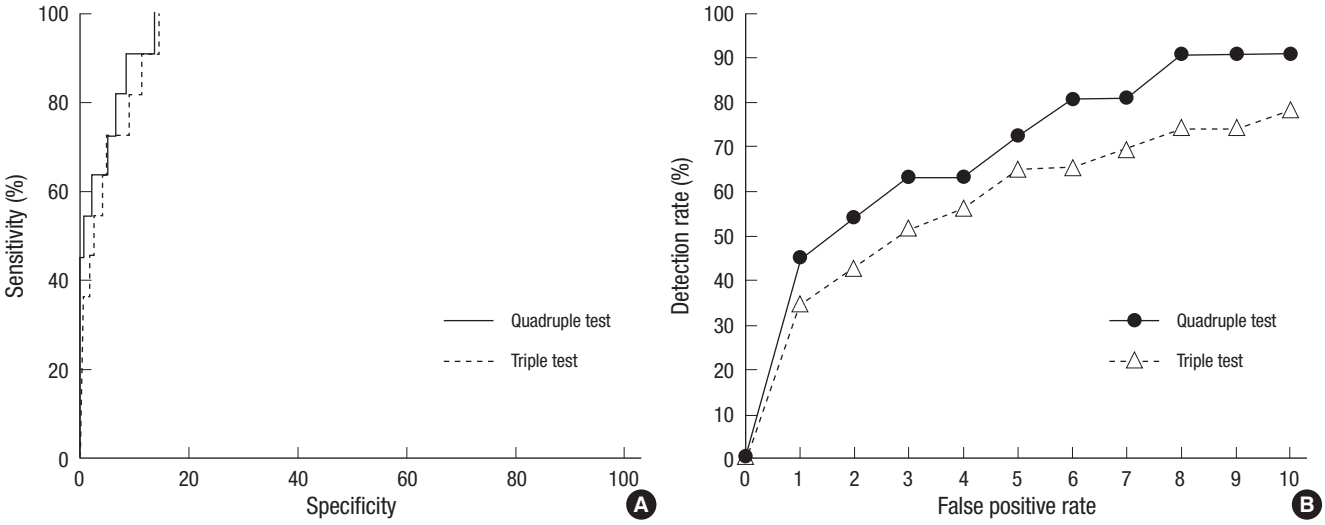

Fig. 1. Screening perfomances of triple and quadruple screening for Down syndrome risk. (**A**) ROC curve of quadruple screening (AUROC, 0.966; 95% confidence interval [CI], 0.940-0.991) and triple screening (AUROC, 0.955; 95% CI, 0.927-0.983) for Down syndrome risk. (**B**) Down syndrome detection and false-positive rates for quaduple and triple test.

Table 4. Screening performance for Down syndrome with second trimester screening tests according to various risk cut-off values

Screening	Risk cutoff														
	1 in 150			1 in 200			1 in 250			1 in 270			1 in 300		
	DR	FPR	OAPR	DR	FPR	OAPR	DR	FPR	OAPR	DR	FPR	OAPR	DR	FPR	OAPR
Triple	52.2	3.2	1: 40	60.8	4.7	1: 55	65.2	6.1	1: 66	65.2	6.7	1: 69	69.6	7.3	1: 73
Quadruple	72.7	4.7	1: 47	72.7	5.8	1: 57	81.8	6.6	1: 59	81.8	6.8	1: 62	81.8	7.2	1: 64

DR, detection rate (%); FPR, false-positive rate; OAPR, odds of being affected given a positive result.

Table 5. Screening performances of triple and quadruple tests using dataset of this study compared with the HIT program

Screening	HIT program (Cut off value 1:270)	Program of this study (Cut off value 1:250)
Triple screening		
Detection rate	66.7%	65.2%
False positive rate	7.3%	6.1%
Quadruple screening		
Detection rate	81.8%	81.8%
False positive rate	7.8%	6.6%

The serum marker levels were converted to MoMs according to gestational age and maternal weight and then the MoM level of each serum marker was compared between gravidas with pregnancies complicated by Down syndrome and gravidas with unaffected pregnancies. The mean MoM levels of AFP and uE3 in pregnancies complicated by Down syndrome were significantly lower than in unaffected pregnancies ($P = 0.012$ and $P = 0.001$, respectively). In addition, the mean MoM levels of hCG and inhibin A in pregnancies complicated by Down syndrome were significantly higher than in unaffected pregnancies ($P = 0.001$ and $P < 0.001$, respectively; Table 3). The medians and standard deviations of the log-Gaussian distribution for each serum marker are summarized in Table 3. For Korean and Caucasian women with pregnancies complicated by Down syndrome (17), the MoMs of serum markers were 0.82 and 0.74 for AFP, 1.80 and 2.05 for hCG, 0.74 and 0.70 for uE3, and 2.543 and 2.54 for inhibin A, respectively.

Screening performance for second trimester screening tests

Using the statistical distributions for each marker, we calculated screening performances for triple and quadruple screenings. Fig. 1 shows the 'ROC curves' that gives the detection and false-positive rates for the triple and quadruple tests. The AUROC curve was highly significant ($P < 0.001$) for quadruple (AUROC, 0.966; 95% confidence interval [CI], 0.940-0.991) and triple tests (AUROC, 0.955; 95% CI, 0.927-0.983). Table 4 shows the observed screening performances of triple and quadruple tests according to various risk cut-off values. The quadruple test achieved a Down syndrome detection rate of 81.8%, and the odds of being affected given a positive result (OAPR) of 1:59 at a risk cut-off value of 1:250. The triple test achieved a Down syndrome detection rate of 69.5% at a risk cut-off value of 1:300, and the OAPR was 1:73.

When the screening performance using our dataset was compared with the screening performance using the HIT program, triple screening showed a slight decrease in the detection rate from 66.7% to 65.2%, but a larger decrease in the false-positive rate from 7.3% to 6.1%. Quadruple screening also lowered the false-positive rate from 7.8% to 6.6% while maintaining the de-

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tection rate at 81.8% (Table 5).

DISCUSSION

This study established a parameter set of serum markers for triple and quadruple screening tests in pregnant Korean women. This can improve the screening performance of pregnancies complicated by Down syndrome compared with the previous programs based on a parameter set for Western women. In the current study, the detection rates of triple and quadruple screening were 65.2% and 72.7%, respectively, at a false-positive rate of 5%. Compared with the current program, the screening performance using our dataset was much improved.

In Korea, the second trimester screening tests have used a cut-off value of 1:270 since the screening test was implemented. When the serum screening markers were under development, a cut-off value of 1:270 was used to maintain consistency with the existing cut-off value for previous screening using maternal age only, but nowadays when various screening programs are available, it is not appropriate to apply a cut-off value of 1:270 uniformly without considering the screening performance of each program. The risk cut-off of a screening test should be set specifically to each country in consideration of the performance of the screening test, the cost and safety of invasive diagnostic procedures, the prevalence of Down syndrome, and the age distribution of pregnant women in the country. The optimal cut-off value for the quadruple screening test using our parameter set is considered to be 1:250 (detection rate of 81.8% at a false-positive rate of 6.6%). In our analysis, a lower cut-off value of 1:350 led to 79 additional amniocenteses and resulted in the detection of 1 additional case of fetal Down syndrome. To improve the detection rate, adopting the first trimester combined screening may be efficient rather than lowering the cut-off value in the second trimester screeing test. Recent studies have suggested that a combination of first trimester screening and second trimester quadruple screening achieved a detection rate of 94%-96% at a false-positive rate of 5% (17, 18).

In the current study, the concentrations of AFP, hCG, uE3, and inhibin A were higher on average than the concentrations established for the Caucasian population. Ethnic differences have been noted in comparisons of black, Caucasian, and Asian populations in Europe and the USA (11, 18, 20). It is known that Asian women have the highest levels of AFP, hCG, and uE3 (11, 13), and our study was in line with the previous studies. In addition, we emphasize that the serum level of inhibin A is also the highest in Asian women (9). With respect to inhibin A, even though some studies have reported that black women have higher levels of inhibin A than Caucasian women (20), a comparison between Asian and Caucasian women has not been attempted thus far. Although the ethnic effect on screening for Down syndrome appears to be relatively minor because of the counterbalancing effect of multiple serum markers (12), correction for ethnicity can have a significant impact on individual risk, which could alter clinical decision-making (20).

The median MoM of hCG in Korean women with a Down syndrome pregnancy was 1.80, which was lower compared to 2.01-2.12 in Caucasian women (21). In Chinese women, the median MoM of hCG in Down syndrome pregnancies was 1.4 (13). Although these studies were limited by small sample sizes, the median MoM of each serum marker in Down syndrome pregnancies may reflect racial differences. Further research with larger samples of pregnancies complicated by Down syndrome is needed.

Meanwhile, factors affecting the performance of Down syndrome screening include the use of ultrasound scans to estimate gestational age, maternal weight, insulin-dependent diabetes, and smoking (21-25). Of these factors, insulin-dependent diabetes and smoking were not taken into account in this study, as the prevalence of insulin-dependent diabetics in Korea is extremely low, with a prevalence of 1.4 per 100,000, and very few Korean pregnant women smoke cigarettes.

In conclusion, we introduce a more accurate and efficient screening method for antenatal Down syndrome screening based on a Korean-specifc parameter set. With the proposed parameter model, quadruple screening can detect 81.8% of pregnancies complicated by Down syndrome in the second trimester with a false-positive rate of 6.6% at a cut-off value of 1:250 in Korea. Future research is needed to develop the specified guideline of genetic counseling based on the larger samples for Korean women.

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AUTHOR SUMMARY

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In Korea, the triple and quadruple screening tests for pregnancies complicated with Down syndrome have been used widely. However, little information is available on the performance of these screening tests for Korean women. In this large population study, we introduced a more accurate and efficient screening method for antenatal Down syndrome screening based on a Korean-specific parameter set.

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