

SCREENING OF MATERNAL SERUM FOR FETAL DOWN'S SYNDROME  
IN THE FIRST TRIMESTERJAMES E. HADDOW, M.D., GLENN E. PALOMAKI, B.S., GEORGE J. KNIGHT, PH.D., JOSEPHINE WILLIAMS,  
WAYNE A. MILLER, M.D., AND ANTHONY JOHNSON, D.O.**ABSTRACT**

**Background** Screening of maternal serum to identify fetuses with Down's syndrome is now routinely offered during the second trimester of pregnancy. Prenatal screening by means of serum assays or ultrasonographic measurements, either alone or in combination, may also be possible in the first trimester.

**Methods** We measured serum alpha-fetoprotein, unconjugated estriol, human chorionic gonadotropin (hCG), the free beta subunit of hCG, and pregnancy-associated protein A in 4412 women (82 percent of whom were 35 years of age or older) who came to 16 prenatal diagnostic centers for chorionic-villus sampling or early amniocentesis at 9 to 15 weeks of gestation. Ultrasound measurements of fetal nuchal translucency were also reported. Fetal chromosomal analysis was performed in all pregnancies. Altogether, there were 61 fetuses with Down's syndrome.

**Results** A total of 48 pregnancies affected by Down's syndrome and 3169 unaffected pregnancies were identified before 14 weeks of gestation; the rates of detection of Down's syndrome for the five serum markers were as follows: 17 percent for alpha-fetoprotein, 4 percent for unconjugated estriol, 29 percent for hCG, 25 percent for the free beta subunit of hCG, and 42 percent for pregnancy-associated protein A, at false positive rates of 5 percent. The results of the measurements of serum hCG and its free beta subunit were highly correlated. When used in combination with the serum concentration of pregnancy-associated protein A and maternal age, the detection rate was 63 percent for hCG (95 percent confidence interval, 47 to 76 percent) and 60 percent for its free beta subunit (95 percent confidence interval, 45 to 74 percent). Measurements of nuchal translucency varied considerably between centers and could not be reliably incorporated into our calculations.

**Conclusions** Screening for Down's syndrome in the first trimester is feasible, with use of measurements of pregnancy-associated protein A and either hCG or its free beta subunit in maternal serum. (N Engl J Med 1998;338:955-61.)

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**A**PPROXIMATELY 2.5 million pregnant women now undergo screening of serum for Down's syndrome each year in the United States.<sup>1</sup> Nearly all this testing is carried out in the second trimester. The first serum marker found to be associated with Down's syndrome was alpha-fetoprotein, the measurement of

which was already being used as a screening test for open neural-tube defects.<sup>2-4</sup> In 1987 and 1988, other serum markers were found to improve the sensitivity of screening, notably human chorionic gonadotropin (hCG)<sup>5</sup> and unconjugated estriol.<sup>6</sup> The discovery of these markers was based on case-control studies using stored second-trimester serum samples from pregnant women who were screened for fetal neural-tube defects.<sup>7</sup> The studies demonstrated that maternal serum alpha-fetoprotein and unconjugated estriol concentrations were lower and hCG concentrations higher in the presence of a fetus with Down's syndrome than when the fetus was unaffected.

The initial indication that first-trimester screening for Down's syndrome might be possible came in 1986,<sup>8</sup> when maternal serum alpha-fetoprotein concentrations were reported to be relatively low in the presence of Down's syndrome at 9 to 12 weeks' gestation. Subsequent studies examined other potential serum markers that could be measured during the first trimester.<sup>9-11</sup> The two most promising of these (serum concentrations of the free beta subunit of hCG<sup>11</sup> and pregnancy-associated protein A),<sup>12</sup> when combined, were estimated to yield a rate of detection of Down's syndrome<sup>13</sup> that approached that of the three serum tests now commonly used during the second trimester.<sup>14</sup> Serum concentrations of the free beta subunit of hCG are higher than average, and pregnancy-associated protein A concentrations are lower, in the presence of a fetus with Down's syndrome. In 1992, nuchal translucency, as measured by ultrasonography in the first trimester, was found to be thicker in fetuses with Down's syndrome than in unaffected fetuses.<sup>15</sup> Subsequently, this measurement has been reported to be effective for screening when the test is performed by specially trained physicians.<sup>16,17</sup> In this prospective, noninterventive study, we further examined the efficacy of serum and ultrasound screening for Down's syndrome in the first trimester and the possible advantages and disadvantages of screening at this time rather than during the second trimester.

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## METHODS

### Study Subjects

Between June 1994 and November 1996, we measured serum concentrations of alpha-fetoprotein, unconjugated estriol, hCG, the free beta subunit of hCG, and pregnancy-associated protein A in 4412 women with singleton pregnancies who were referred to 16 prenatal diagnostic centers in the United States (see Appendix 1) for chorionic-villus sampling or amniocentesis. The women ranged in age from 15 to 51 years (median, 37 years; 82 percent were 35 or older); 76 percent were non-Hispanic white, 10 percent were Hispanic, 9 percent were Asian, 1 percent were black, and the race or ethnic group of 4 percent was unknown or other. The indications for the diagnostic procedure were advanced maternal age (87 percent), a family history of Down's syndrome (4 percent), a family history of another chromosomal abnormality (3 percent), a family history of another genetic disorder (2 percent), and a variety of other indications (4 percent). Less than 1 percent of the women were referred because of abnormal findings on ultrasonography or exposure to a teratogen, and none were referred because of a positive serum screening test. The largest site enrolled 16 percent of the women; the smallest, 1.3 percent. Each woman reported her date of birth, race or ethnic background, weight, and other demographic and pregnancy-related information. Gestational age was estimated by ultrasonography as well as by the date of the last menstrual period for all the pregnancies. The thickness of fetal nuchal translucency was measured by ultrasonography according to a published protocol in 4049 of the women.<sup>15</sup> The study was approved by the institutional review board of the study's coordinating center and also by the appropriate oversight committees at the 16 participating prenatal diagnostic centers. All the women gave informed consent.

### Collection of Samples

A blood sample was obtained before chorionic-villus sampling or early amniocentesis, and the serum was separated and refrigerated until it was sent by overnight mail to the study center in Scarborough, Maine, for biochemical analysis. The laboratory measurements were performed within two working days after receipt of the sample, but the results were not made available for clinical purposes. The prenatal diagnostic centers subsequently sent the results of karyotype analysis of the cells obtained by chorionic-villus sampling or amniocentesis in all 4412 women to the study center. Inherited balanced translocations, pseudo-mosaicism, normal variants, and common inversions were among the findings in the 4242 pregnancies with normal karyotypes.

### Serum Measurements

Serum alpha-fetoprotein and the free beta subunit of hCG were measured with a fluoroimmunoassay (Delfia hAFP/Free hCG $\beta$  Dual kit; Wallac Oy, Turku, Finland). Serum unconjugated estriol was measured with the Ultra-Sensitive Unconjugated Estriol kit (Diagnostic Systems Laboratories, Webster, Tex.); the sensitivity of the assay was increased by doubling the sample volume, increasing the incubation time by 30 minutes, and adding a lower standard at 0.05 ng per milliliter. Serum hCG was measured with the hCG MAlAclone assay (Biodata Diagnostics, Rome). Serum pregnancy-associated protein A was measured with an in-house enzyme-linked immunosorbent assay (ELISA) with use of a commercially available antibody (Dako, Glostrup, Denmark). The interassay coefficients of variation were 10 percent or less for all five assays.

### Statistical Analysis

At intervals during enrollment, median values were calculated for each of the five serum markers. Median values for each day were derived separately, according to whether gestational ages were based on ultrasonography or on the date of the last menstrual period. Individual values were expressed as multiples of these median values for each woman. Among the ultrasound

measurements available for dating purposes, measurements of the biparietal diameter were preferred, followed by crown-rump length and composite measurements. The values, expressed as multiples of the median, were adjusted for maternal weight with equations from a published protocol.<sup>18</sup> For each center, we computed the median and 95th percentile of nuchal-translucency measurements in pregnancies in which the fetus was unaffected and then tallied the percentage of cases of Down's syndrome with measurements above the 95th percentile.

### Determining the Risk of Down's Syndrome

The risk according to maternal age (expressed as the odds of Down's syndrome in the fetus) was estimated with use of a published equation.<sup>19</sup> For example, the odds that a 35-year-old woman will deliver a baby with Down's syndrome are 1:385. Those odds are then converted to first-trimester odds ( $1:385 \times 0.55 = 1:212$ ) to account for the 45 percent of fetuses with Down's syndrome that would be spontaneously lost between the first trimester and term.<sup>20</sup> The modified odds of delivering a baby with Down's syndrome are then computed by multiplying the age-specific odds by the likelihood ratio derived from the woman's analyte measurements.<sup>7</sup> These odds are then used to classify pregnancies as either high-risk or low-risk. The underlying model relies on overlapping multivariate gaussian distributions<sup>7</sup> and has been described in more detail elsewhere.<sup>14</sup> Its application to first-trimester testing requires that appropriate values (means, standard deviations, and correlation coefficients) be defined for each marker in unaffected pregnancies and pregnancies affected by Down's syndrome. The detection rate is defined as the percentage of pregnancies affected by Down's syndrome with odds at or above a specified cutoff value. The associated false positive rate is defined as the percentage of unaffected pregnancies with odds at or above that same cutoff level. Confidence intervals for the observed rates of detection were computed on the basis of the binomial distribution.

Logistic-regression analysis was also performed to verify the reliability of the gaussian model. Two logistic models were fitted — one with serum concentrations of pregnancy-associated protein A and hCG and the other with serum concentrations of pregnancy-associated protein A and the free beta subunit of hCG. All measurements were expressed as multiples of the median. Neither model included interaction terms. As in the gaussian model, maternal age was used to assign prior risk. The odds derived from the logistic model were then used to calculate the odds ratio for each pregnancy. That value, in turn, was multiplied by the prior risk to determine the odds that the fetus had Down's syndrome.

## RESULTS

Results of fetal chromosomal analysis were available for all 4412 pregnancies. The total numbers of women with unaffected pregnancies and pregnancies affected by Down's syndrome who were tested at each completed week of gestation from 9 through 15 weeks (dated by ultrasonography) were 72 and 1 at 9 weeks, 777 and 10 at 10 weeks, 1204 and 18 at 11 weeks, 486 and 11 at 12 weeks, 630 and 8 at 13 weeks, 855 and 11 at 14 weeks, and 218 and 2 at 15 weeks. An additional 109 pregnancies with other chromosomal abnormalities were also identified.

Our initial analysis of the serum markers included all the women. The serum concentrations of all five markers changed with the length of gestation, but not with maternal age. The serum concentrations of alpha-fetoprotein, unconjugated estriol, and pregnancy-associated protein A fitted a log-linear model; the median concentrations increased by 33 percent, 49 percent, and 37 percent per week, respectively.

**TABLE 1.** MEDIAN CONCENTRATIONS OF FIVE SERUM MARKERS IN WOMEN WHOSE FETUSES HAD DOWN'S SYNDROME, ACCORDING TO WEEK OF GESTATION.

Wk OF GESTATION	NO. OF CASES OF DOWN'S SYNDROME	VALUE*				
		ALPHA-FETOPROTEIN	UNCONJUGATED ESTRIOL	hCG	FREE BETA SUBUNIT OF hCG	PREGNANCY-ASSOCIATED PROTEIN A
9-13	48	0.85	1.00	1.54	2.08	0.41
9-11	29	0.88	1.06	1.38	2.31	0.36
12-13	19	0.78	0.95	1.88	1.99	0.48
14-15	13	0.72	0.64	1.88	3.26	0.72

\*Values shown are median multiples of the median serum concentration in the women whose fetuses were unaffected. hCG denotes human chorionic gonadotropin.

The serum concentrations of hCG and its free beta subunit fitted a linear model. For example, the median serum concentrations decreased by 13 percent and 16 percent, respectively, between 11 and 12 weeks of gestation.

There was a high degree of correlation between measurements of serum hCG and its free beta subunit in unaffected pregnancies ( $r=0.8$ ) and in pregnancies affected by Down's syndrome ( $r=0.7$ ). This level of correlation precludes the two analytes' being used together for screening purposes. Serum concentrations of pregnancy-associated protein A, however, were relatively independent of hCG and its free beta subunit, thus allowing pregnancy-associated protein A to be combined with either of them.

The median serum concentrations of each marker in pregnancies affected by Down's syndrome are shown in Table 1 at several intervals during gestation. These concentrations are expressed as multiples of the respective median serum concentrations in unaffected pregnancies. The median serum concentrations of alpha-fetoprotein and unconjugated estriol were more discriminatory as gestation advanced. At 14 to 15 weeks of gestation, the values approximate those found in the second trimester. The median serum concentrations of hCG and its free beta subunit were slightly lower than the concentrations found later in pregnancy. The median serum concentration of pregnancy-associated protein A was lowest early in the first trimester and became less discriminatory as gestation advanced. Although the difference in median values for pregnancy-associated protein A before and after 14 weeks is not statistically significant (0.41 vs. 0.72 multiple of the median,  $P=0.12$ ), it is consistent with reports that measurements of serum pregnancy-associated protein A are not useful for screening purposes in the second trimester.<sup>21,22</sup> Therefore, the remaining analyses of performance of screening were restricted to the 48 pregnancies affected by Down's syndrome and the 3169 unaffected pregnancies that

were studied before 14 weeks of gestation. Not shown are the median serum concentrations of the five markers for the 109 pregnancies in which the fetuses had other chromosomal abnormalities. Only three occurred in 10 or more pregnancies (trisomy 18, balanced translocations, and inversions), and only trisomy 18 was associated with sufficiently abnormal measurements that screening might be possible. The median serum concentrations of hCG, its free beta subunit, and pregnancy-associated protein A in pregnancies in which the fetus had trisomy 18 were 0.31, 0.22, and 0.30 multiple of the median, respectively, in relation to median values for unaffected pregnancies.

The rates of detection of Down's syndrome were low for serum alpha-fetoprotein and unconjugated estriol (17 percent and 4 percent, respectively, at a 5 percent false positive rate), and these two markers were therefore not included in subsequent analyses. The rates of detection were higher for serum hCG (29 percent; 95 percent confidence interval, 17 to 44 percent), the free beta subunit of hCG (25 percent; 95 percent confidence interval, 14 to 40 percent), and pregnancy-associated protein A (42 percent; 95 percent confidence interval, 28 to 57 percent) at a 5 percent false positive rate. These formed the basis for our subsequent analyses of the value of screening.

The rates of detection of pregnancies affected by Down's syndrome when we used measurements of serum hCG combined with serum pregnancy-associated protein A or the free beta subunit of hCG along with serum pregnancy-associated protein A, each at a 5 percent false positive rate, are shown in Table 2. The rates are based on the actual values and maternal ages of the 48 women whose fetuses were affected by Down's syndrome and the 3169 with unaffected pregnancies. The rates of detection were similar for the two combinations of markers. We obtained these values with the gaussian model by combining the prior odds of Down's syndrome, based on

**TABLE 2.** DETECTION OF DOWN'S SYNDROME WITH TWO COMBINATIONS OF MATERNAL SERUM MARKERS AT 9 THROUGH 13 WEEKS' GESTATION.

FALSE POSITIVE RATE	DETECTION RATE (95% CI)*	
	MATERNAL AGE, SERUM hCG, AND PAP-A	MATERNAL AGE, SERUM hCG FREE BETA SUBUNIT, AND PAP-A
	percent	
5	63 (47-76)	60 (45-74)
10	71 (56-83)	65 (49-78)
15	77 (63-88)	73 (58-85)
20	83 (70-93)	83 (70-93)
25	85 (72-94)	85 (72-94)

\*The detection rate is the percentage of the 48 cases of Down's syndrome detected with use of the combination of markers. CI denotes confidence interval, hCG human chorionic gonadotropin, and PAP-A pregnancy-associated protein A.

maternal age, with the serum concentrations of pregnancy-associated protein A and either hCG or its free beta subunit. (Appendix 2 lists the parameters used in these calculations.) To verify the estimates derived from the gaussian model, we applied logistic-regression analysis to the same data set. According to this model, at a 5 percent false positive rate, the rate of detection of Down's syndrome for serum pregnancy-associated protein A in combination with serum hCG was 58 percent, and that for serum pregnancy-associated protein A plus the serum free beta subunit of hCG was 60 percent. The detection rates were also similar at the other false positive rates listed in Table 2. Adding maternal age and the three first-order interaction terms to the logistic model yielded similar results (data not shown).

The nuchal-translucency measurements are shown according to mean gestational age in Table 3. Nuchal-translucency measurements were attempted in 3991 normal pregnancies and 58 affected by Down's syndrome. Measurements were obtained in 61 to 100 percent of the pregnancies at the different centers (average, 83 percent). The median nuchal-translucency thickness ranged from 1.0 mm to 4.0 mm at the different centers (the expected median value is approximately 1.5 mm and is known to increase with gestational age).<sup>23</sup> The overall rate of detection of Down's syndrome (based on a criterion of nuchal-translucency measurements above the 95th percentile for each center) was 31 percent, with a 5 percent false positive rate. The variability among centers in median values and in the ratios of the 95th percentile to the 50th percentile, coupled with their vary-

ing ability to obtain the measurements successfully, suggests that the performance of this indicator in our study might not accurately reflect its long-term performance at individual centers. For this reason, the nuchal-translucency measurements were not included with the results of the serum assays in our analysis.

## DISCUSSION

The association between Down's syndrome and elevated maternal serum hCG concentrations in the first trimester has been the subject of at least 17 reports (including the current study) covering a total of 396 affected pregnancies.<sup>13,24-38</sup> Overall, the maternal hCG values in pregnancies in which the fetus has Down's syndrome are 28 percent higher (95 percent confidence interval, 17 to 39 percent), but individual point estimates of the difference range from -9 percent to 83 percent. Our estimate (56 percent) ranks third highest among those in the 17 studies. One possible explanation is that measurements of serum hCG made earlier in the first trimester are less sensitive in predicting Down's syndrome than those obtained later. In a number of studies, many of the samples were obtained from women who were less than 10 weeks pregnant, whereas very few of our samples were collected that early. According to our data, measurement of hCG in maternal serum is as effective as measurement of its free beta subunit in screening for Down's syndrome at 10 through 13 weeks of gestation.

Our estimates of the performance of screening tests are based on gestational dates determined by ultrasonography, which are more reliable than the dates determined on the basis of the last menstrual period. On the basis of studies during the second trimester, the use of the date of the last menstrual period to calculate gestational age would reduce the rate of detection of Down's syndrome by 3 to 5 percent.<sup>39</sup> Gestational age needs to be established by ultrasonography in the first trimester, because serum concentrations of pregnancy-associated protein A change rapidly during that time. None of the concentrations of serum markers used for screening during the second trimester change as rapidly, so the date of the last menstrual period can be used at that time.

The combination of serum concentrations of the free beta subunit of hCG and pregnancy-associated protein A has been recognized for several years as suitable for screening for Down's syndrome in the first trimester. In spite of this, however, screening of maternal serum for Down's syndrome in the first trimester is not widespread. Yet there are potential advantages to screening at this earlier time. The psychological effects of identifying an affected pregnancy are likely to be less severe, and the termination of pregnancy, if chosen, is associated with a lower risk to the mother.<sup>40</sup> There are several possible explana-

**TABLE 3.** DETECTION OF DOWN'S SYNDROME BY MEASUREMENTS OF FETAL NUCHAL TRANSLUCENCY.

CENTER	MEAN GESTATIONAL AGE	MEASUREMENT ATTEMPTED	SUCCESS RATE	THICKNESS OF NUCHAL TRANSLUCENCY		DETECTED CASES*
				50TH PERCENTILE	95TH PERCENTILE	
	wk	no. of pregnancies	%	mm		% (no. detected/total no.)
1	11.0	317	76	2.0	3.0	20 (1/5)
2	11.2	198	98	1.5	3.3	29 (2/7)
3	11.2	134	90	1.8	2.8	100 (1/1)
4	11.3	367	63	1.4	3.8	25 (2/8)
5	11.3	238	99	1.5	2.4	100 (2/2)
6	11.3	337	61	1.0	2.6	33 (2/6)
7	11.3	327	99	2.0	3.0	0 (0/5)
8	11.4	51	84	1.1	2.0	100 (1/1)
9	11.4	19	74	1.1	3.0	— (0/0)
10	11.7	84	100	1.8	2.6	0 (0/3)
11	11.7	57	86	1.5	4.2	100 (1/1)
12	13.0	98	98	1.9	2.9	— (0/0)
13	13.4	211	90	2.4	4.0	0 (0/2)
14	13.7	697	65	2.0	5.0	50 (3/6)
15	13.9	256	89	2.5	5.0	33 (1/3)
16	14.2	600	99	4.0	4.9	25 (2/8)
Total	—	3991	83	—	—	31 (18/58)

\*For each center, the number of cases of Down's syndrome with nuchal-translucency measurements at or above the 95th percentile was divided by the total number of cases for which a nuchal-translucency measurement was attempted. In nine of the cases, nuchal-translucency measurements were attempted but were unsuccessful.

tions for the fact that screening for Down's syndrome has not been widely conducted during the first trimester. Chorionic-villus sampling and early amniocentesis are not as widely available as amniocentesis during the second trimester, and they may be less safe. Screening for Down's syndrome in the first trimester, followed by screening for open neural-tube defects during the second, is likely to be less cost effective than doing all the screening at the same time.<sup>41</sup> About 20 percent of fetuses with Down's syndrome are lost spontaneously between 10 and 16 weeks of gestation. In order for first-trimester screening for Down's syndrome to be similar to second-trimester screening in terms of sensitivity, gestational age needs to be established by ultrasonography. Finally, assays for serum pregnancy-associated protein A and the free beta subunit of hCG are not licensed for clinical use in the United States. The unavailability of assays for the free beta subunit is no longer a barrier, since the measurement of hCG in serum is a suitable substitute.

It may be possible to overcome at least some of the remaining barriers to the implementation of first-trimester screening. For example, the necessary assays are likely to become more widely available in the future, and it may be possible to reduce the costs

associated with routine ultrasound dating by redefining and narrowing the scope of the examination. In the future, nuchal-translucency measurements might be used in conjunction with serum measurements, with the added costs offset by the improved performance of screening. This would require standardization and ongoing control of the quality of the ultrasound measurements (as is already the case with serum screening) and evidence that nuchal-translucency measurements could be performed reliably in primary care facilities in the United States; it has not yet been shown that nuchal-translucency measurements can be done properly in such settings. Our study provides evidence that first-trimester screening of maternal serum to determine the risk of fetal Down's syndrome is feasible when serum pregnancy-associated protein A concentrations are used in combination with the concentration of either hCG or its free beta subunit.

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**APPENDIX 1. STUDY CENTERS**

The collaborating prenatal diagnostic centers and the study investigators were as follows: South West Genetics, San Antonio, Tex. — G. Khodr; Prenatal Diagnostic and Imaging Center, Sacramento, Calif. — F.W. Hanson; University of Tennessee, Memphis — L. Shulman; University of California, San Francisco — J.D. Goldberg; Thomas Jefferson University, Philadelphia — A. Johnson and R.J. Wapner; Prenatal Diagnostic Center of Southern California, Beverly Hills — J. Williams III; University of Iowa, Iowa City — R.A. Williamson; Maine Medical Center, Portland — M.G. Pinette; Arizona Institute for Genetics and Fetal Medicine, Chandler — G. Simpson; Swedish Medical Center, Seattle — D.A. Luthy; University of Maryland, Baltimore — C. Meyers; Prenatal Diagnostic Center, Lexington, Mass. — W.A. Miller and A. Johnson; Pennsylvania Hospital, Philadelphia — A.E. Donnenfeld; University Hospital, Seattle — E. Cheng; Strong Memorial Hospital, Rochester, N.Y. — D.N. Saller, Jr.; Baylor College of Medicine, Houston — J.L. Simpson.

**APPENDIX 2. PARAMETERS**

The table below shows the parameters for serum hCG, the free beta subunit of hCG, and pregnancy-associated protein A used in calculating likelihood ratios for Down's syndrome at 9 through 13 weeks of gestation. The values of the markers fit a log gaussian distribution, at least between the 5th and 95th percentiles, with the exception of pregnancy-associated protein A in pregnancies with Down's syndrome (which fit well between the 10th and 80th percentiles). The median multiple of the median for unaffected pregnancies is 1.0, by definition, for all markers (or a logarithmic median of 0). The table also shows truncation limits for each of the markers. These limits are necessary to avoid computing inappropriate likelihood ratios for Down's syndrome when a measurement falls in the extreme tail of a distribution (e.g., the 99th percentile of any of the markers) or in a region in which the model does not fit the data well (e.g., the 5th percentile of pregnancy-associated protein A).

POPULATION DATA FOR THREE SERUM MARKERS.\*

VARIABLE AND MARKER	3169 UNAFFECTED PREGNANCIES	48 PREGNANCIES WITH DOWN'S SYNDROME
<b>Log median</b>		
hCG	0.000	0.178
Free beta subunit	0.000	0.311
Pregnancy-associated protein A	0.000	-0.370
<b>Log SD</b>		
hCG	0.188	0.175
Free beta subunit	0.275	0.257
Pregnancy-associated protein A	0.251	0.272
<b>Correlation coefficient</b>		
hCG and free beta subunit	0.752	0.647
hCG and pregnancy-associated protein A	0.170	0.121
Free beta subunit and pregnancy-associated protein A	0.154	-0.038
<b>Truncation limits</b>		
hCG	0.6-3.0	
Free beta subunit	0.5-5.0	
Pregnancy-associated protein A	0.2-2.0	

\*Values have been adjusted for the week of gestation, as determined by ultrasonography, and for maternal weight. Log median denotes the base 10 log of the median value (expressed as a multiple of the median), log SD the standard deviation of the base 10 log-transformed value (expressed as a multiple of the median), and hCG human chorionic gonadotropin. Truncation limits are expressed in multiples of the median value.

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