First-Trimester Screening for Trisomies 21 and 18

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ABSTRACT

BACKGROUND

Screening for aneuploid pregnancies is routinely performed after 15 weeks of gestation and has a sensitivity of approximately 65 percent, with a false positive rate of 5 percent. First-trimester markers of aneuploidy have been developed, but their use in combination has not been adequately evaluated in clinical practice.

METHODS

We conducted a multicenter study of screening for trisomies 21 and 18 among patients with pregnancies between 74 and 97 days of gestation, based on maternal age, maternal levels of free β human chorionic gonadotropin and pregnancy-associated plasma protein A, and ultrasonographic measurement of fetal nuchal translucency. A screening result was considered to be positive for trisomy 21 if the calculated risk was at least 1 in 270 pregnancies and positive for trisomy 18 if the risk was at least 1 in 150.

RESULTS

Screening was completed in 8514 patients with singleton pregnancies. This approach to screening identified 85.2 percent of the 61 cases of Down's syndrome (95 percent confidence interval, 73.8 to 93.0), with a false positive rate of 9.4 percent (95 percent confidence interval, 8.8 to 10.1). At a false positive rate of 5 percent, the detection rate was 78.7 percent (95 percent confidence interval, 66.3 to 88.1). Screening identified 90.9 percent of the 11 cases of trisomy 18 (95 percent confidence interval, 58.7 to 99.8), with a 2 percent false positive rate. Among women 35 years of age or older, screening identified 89.8 percent of fetuses with trisomy 21, with a false positive rate of 15.2 percent, and 100 percent of fetuses with trisomy 18.

CONCLUSIONS

First-trimester screening for trisomies 21 and 18 on the basis of maternal age, maternal levels of free β human chorionic gonadotropin and pregnancy-associated plasma protein A, and measurement of fetal nuchal translucency has good sensitivity at an acceptable false positive rate.

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SCREENING FOR FETAL ANEUPLOIDY HAS evolved from a risk assessment based on maternal age to the present approach, which uses age and levels of maternal serum analytes. In the second trimester, levels of alpha-fetoprotein, human chorionic gonadotropin, and unconjugated estriol are used to refine estimates of risk based on maternal age, and this approach will identify approximately 65 percent of fetuses with Down's syndrome (trisomy 21), with a false positive rate of 4.5 to 5.0 percent.[1] Measurement of inhibin A has been added by many laboratories and may increase the rate of detection to 75 percent.[2] Serum screening substantially improves the detection rate of 30 percent obtained with the use of maternal age alone. However, delaying screening until the second trimester means that decisions about invasive testing or termination of pregnancy must be deferred accordingly. This delay may be unacceptable to some people, since prenatal diagnosis can be performed during the first trimester by means of chorionic-villus sampling. This method provides maternal privacy, timely reassurance, or the option of earlier and safer termination of pregnancy.

Over the past five years, first-trimester screening approaches have been developed. The use of maternal age and levels of two biochemical analytes — pregnancy-associated plasma protein A and the free β subunit of human chorionic gonadotropin — has resulted in detection rates of 60 to 65 percent for trisomy 21.[3] Ultrasonographic measurement of fetal nuchal translucency, when combined with maternal age, can independently detect 77 percent of cases of trisomy 21, with a similar false positive rate of 5 percent.[4] Mathematical modeling has suggested that combining the measurement of biochemical analytes and nuchal translucency during the first trimester may identify up to 89 percent of cases of Down's syndrome, with a false positive rate of 5 percent.[5] Several small, prospective studies have confirmed this hypothesis, but to our knowledge, large, multicenter investigations have not been reported.[6,7]

METHODS

The study was approved by the institutional review board at each of the 12 participating prenatal diagnostic centers. All participants gave written informed consent.

STUDY POPULATION

Patients of any age with a singleton pregnancy between 74 and 97 days of gestation (according to the crown–rump length) were offered prenatal screening for trisomies 21 and 18 on the basis of maternal age, levels of pregnancy-associated plasma protein A and free β human chorionic gonadotropin, and measurement of nuchal translucency. Major exclusion criteria included multiple gestation, recent vaginal bleeding equivalent to a menstrual period, pregestational diabetes mellitus, and pregnancy resulting from a donor oocyte. Patients with indications for prenatal diagnosis other than a risk of trisomy were also excluded.

BIOCHEMICAL ANALYSIS

Blood for biochemical analysis was collected from each patient, applied to five dots on a filter paper, and mailed to NTD Laboratories in Huntington Station, New York. The samples were prepared and the enzyme-linked immunoadsorbent assay for pregnancy-associated plasma protein A and free β human chorionic gonadotropin was performed as previously described.[6,8] The values for pregnancy-associated plasma protein A and free β human chorionic gonadotropin were divided by the gestational-day–specific medians. The resulting multiples of the median were converted into likelihood ratios calculated from bivariate logarithmic gaussian distributions of normal and affected populations in previous studies.[6]

MEASUREMENTS OF NUCHAL TRANSLUCENCY

Measurements of nuchal translucency were assessed according to the standards of the Fetal Medicine Foundation of London.[4] Sonographers underwent training and certification before participating in the study. Each sonographer participated in a one-day didactic course and then performed 50 scans for review and approval by the Fetal Medicine Foundation. Three additional scans were then videotaped and reviewed. Forty-one sonographers participated.

Three measurements of nuchal translucency were obtained (with the largest used for risk calculation) and converted first to multiples of the median on the basis of the gestational-age–specific standards of the Fetal Medicine Foundation and then to likelihood ratios for trisomies 21 and 18,[4] according to an algorithm developed by the Fetal Medicine Foundation. The complete algorithm for calculating

patient-specific risks of trisomies 21 and 18 with biochemical and nuchal-translucency measurements combined is available through the Fetal Medicine Foundation. The prerequisite for clinical use is participation in a training and quality-assurance program approved by the Fetal Medicine Foundation.

We monitored the nuchal-translucency measurements for quality by periodically comparing our values with the norms of the Fetal Medicine Foundation. The data-coordinating center reported deviations from the mean and the proportions below the 5th and above the 95th percentiles for each center and sonographer. When necessary, remedial education and training of the sonographers was initiated. Details of training and quality management have been reported elsewhere.[9]

RISK DETERMINATION AND PATIENT CARE

Patient-specific risks were calculated for the biochemical measurements alone, for nuchal-translucency measurements alone, and for the combination of the two. For each calculation, the gestational-age–specific risks of trisomies 21 and 18 according to maternal age were multiplied by the likelihood ratio based on the biochemical values, the likelihood ratio based on the nuchal-translucency values, and the product of the biochemical and nuchal-translucency likelihood ratios, respectively.

The patient-specific risk on the basis of maternal age, nuchal-translucency values, and biochemical values was reported to the patient and her referring physician and was available for clinical decision making. To be consistent with the approach used for second-trimester screening, we chose a risk of 1 in 270 pregnancies for trisomy 21 and a risk of 1 in 150 for trisomy 18 as the threshold for a positive result. Decisions about subsequent care were left to the discretion of the patient and physician. We recommended to the referring physicians that all patients continuing their pregnancies into the second trimester undergo maternal serum screening.

Fetal chromosome status was determined by prenatal karyotype analysis if invasive testing was performed or by an evaluation of the phenotype at birth. Information about the outcome of pregnancy was obtained by direct follow-up with the patient and review of the delivery records. An effort was made to determine the karyotype of the fetus in every pregnancy that ended in abortion, death in utero, or stillbirth.

STATISTICAL ANALYSIS

Risk-assessment software, which incorporated the likelihood ratios as described above, was supplied to all centers by NTD Laboratories. The calculated first-trimester risks, biochemical and nuchal-translucency measurements, demographic characteristics, second-trimester biochemical measurements, and outcome data were forwarded to the data-coordinating center. During the study, the risk-assessment software underwent two minor adjustments corresponding to changes in the algorithm used by the Fetal Medicine Foundation and updates of the median biochemical values on the basis of our own data. Seventy-four percent of the patients were screened with use of the most recent version of the software. The risks reported here are those calculated for the patients during the study. The parameters of the distribution of second-trimester serum analyte values reported by Cuckle[10] were used to calculate standardized second-trimester risks from the multiples of the median obtained from the individual centers.

We calculated the sensitivity and specificity of first-trimester screening and the associated false positive and false negative rates. Receiver-operating-characteristic (ROC) curves were graphed, and partial areas under the curves were derived.[11] To estimate the effectiveness of first-trimester screening in the general U.S. population, we modeled our data using 1997 data on live births[12] and data on the gestational-age–specific risk of trisomy 21 at 12 weeks' gestation.[13] SAS software, version 8 (SAS Institute), was used for analysis. All reported P values are two-sided.

RESULTS

PATIENT POPULATION

Blood was drawn from 8816 patients to initiate screening (Fig. 1). Of 8514 patients who completed screening, 102 (1.2 percent) had had a previous pregnancy affected by trisomy 21 or 18, and data for these patients were analyzed separately. The fetal cytogenetic or phenotypic status was unknown for 2.2 percent of patients with positive screening results and 2.3 percent of those with negative screening results, leaving 8216 patients in the primary outcome analysis. Base-line data for these patients are given in Table 1. The mean time from blood collection to risk assessment was eight days.
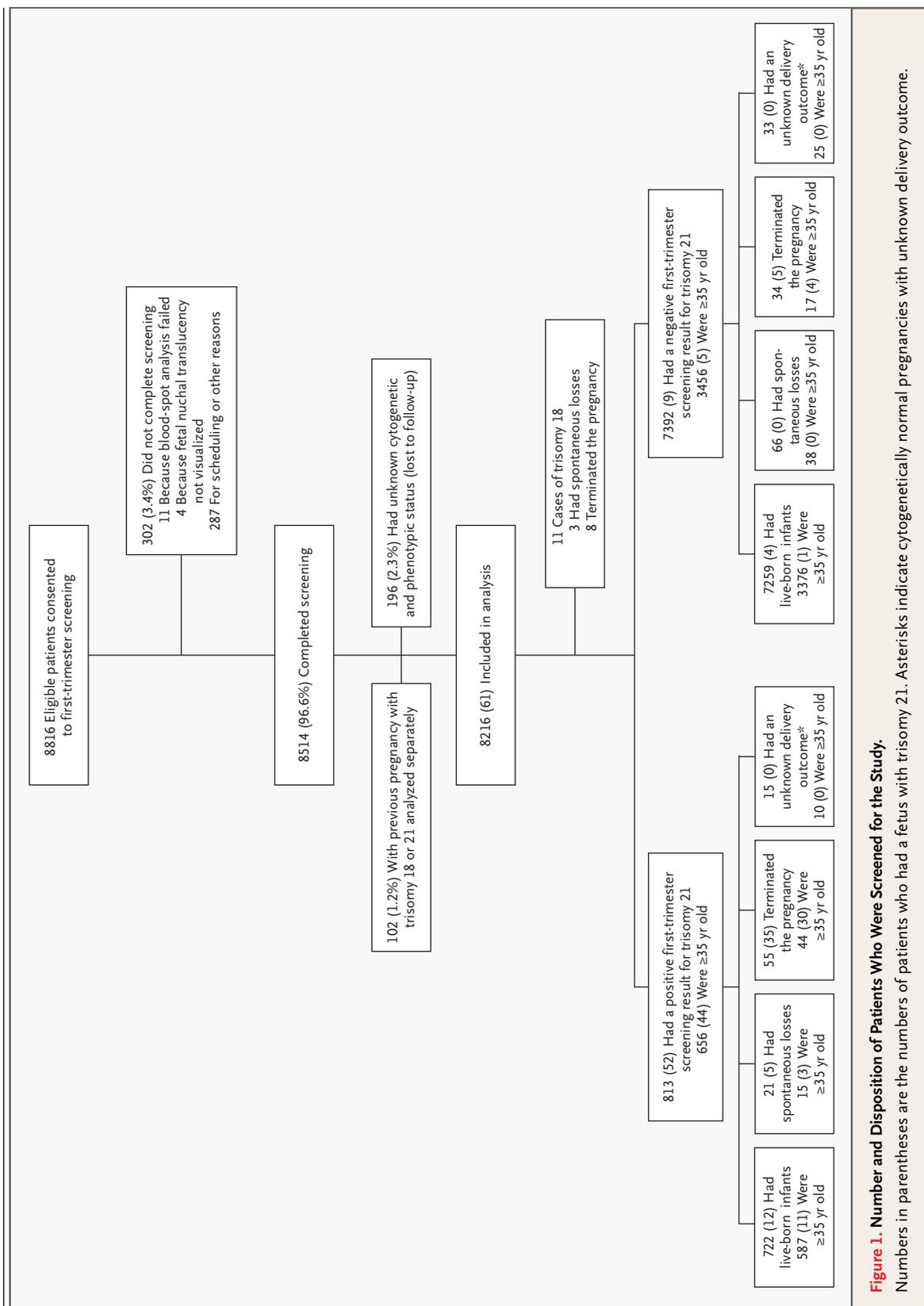
Figure 1. Number and Disposition of Patients Who Were Screened for the Study.

Numbers in parentheses are the numbers of patients who had a fetus with trisomy 21. Asterisks indicate cytogenetically normal pregnancies with unknown delivery outcome.

Ninety patients had spontaneous pregnancy losses. Before 15 weeks of gestation, there were 13 spontaneous losses (cytogenetic analysis, performed in 12 cases, showed trisomy 21 in 2 and a normal karyotype in 10); 33 losses occurred between 15 and 20 weeks of gestation (cytogenetic analysis, performed in 23 cases, showed trisomy 21 in 3 and a normal karyotype in 20). Six losses occurred between screening and 20 weeks of gestation, but the precise time of the loss was unknown (cytogenetic analysis, performed in 5 cases, showed trisomy 18 in 1, triploidy in 1, and a normal karyotype in 3), and 38 losses occurred between 20 weeks and term (cytogenetic analysis, performed in 20 cases, showed trisomy 18 in 2, some other abnormality in 3, and a normal karyotype in 15). For the cases in which cytogenetic analysis was not performed, the phenotype was derived on the basis of pathological analysis.

There were 61 cases of trisomy 21 (prevalence, 1 in 135 pregnancies) and 11 cases of trisomy 18 (prevalence, 1 in 747 pregnancies). Of the 61 pregnancies involving trisomy 21, 5 (8.2 percent) resulted in a spontaneous abortion (2 in week 14 and 3 in week 15), 15 were electively terminated before week 15, 25 were terminated in week 15 or later, and 16 resulted in live births.

MEASUREMENT OF NUCHAL TRANSLUCENCY

Overall, multiples of the median for nuchal-translucency values were 9 percent lower than the expected values established by the Fetal Medicine Foundation on the basis of their analysis of more than 100,000 fetuses[4] (P<0.001); 10.4 percent of our values were less than the 5th percentile of the Fetal Medicine Foundation values and 2.6 percent were greater than the 95th percentile. As the study progressed, our measurements converged toward those of the cohort assessed by the Fetal Medicine Foundation.

ASSESSMENT OF SCREENING

Using a cutoff value of 1:270, we found that the combined approach to screening identified 85.2 percent of the 61 cases of Down's syndrome (95 percent confidence interval, 73.8 to 93.0), with a false positive rate of 9.4 percent (95 percent confidence interval, 8.8 to 10.1). If the cutoff value were adjusted to correlate with a false positive rate of 5 percent (risk 1:129), the sensitivity would be 78.7 percent (95 percent confidence interval, 66.3 to 88.1). A false positive rate of 1 percent would result in the detection of 63.9 percent of cases of Down's syndrome

Table 1. Characteristics of 8216 Pregnant Patients Who Underwent First-Trimester Screening.*

Characteristic	Value
Maternal age at expected date of delivery — no. (%)	
16–24 yr	268 (3)
25–29 yr	1013 (12)
30–34 yr	2815 (34)
35–39 yr	3280 (40)
≥40 yr	840 (10)
Mean maternal age at expected date of delivery — yr	34.5±4.6
Maternal race or ethnic group — no. (%)	
Black	352 (4)
White	6815 (83)
Hispanic	452 (6)
Asian	428 (5)
Other or not reported	169 (2)
Gestational age at screening — no. (%)	
74–76 days	478 (6)
77–83 days	2571 (31)
84–90 days	3223 (39)
91–97 days	1935 (24)
98 days	9 (<1)
Mean gestational age at screening — days	85.7±5.7

* Plus–minus values are means ±SD.

(95 percent confidence interval, 50.6 to 75.8) (Table 2). Although two minor modifications were made to the risk-assessment algorithm during the study, we found no change in the rate of detection and only a 0.1 percent reduction in the false positive rate for trisomy 21 when all risks were recalculated using the most recent version.

Among women 35 years of age or older, the combined approach to screening identified 89.8 percent of the fetuses with trisomy 21, with a false positive rate of 15.2 percent (Table 2). All eight women 35 years of age or older who had a fetus with trisomy 18 were identified by screening. We modeled our results on the expected prevalence of trisomy 21 at birth in the U.S. population. This yielded a rate of detection for trisomy 21 of 78.8 percent, with a 5 percent false positive rate at a cutoff value of 1:337. At a cutoff value of 1:270, 77.5 percent of cases of trisomy 21 would be identified, with a false positive rate of 4.1 percent.

The combined approach to screening identified 90.9 percent of fetuses with trisomy 18 (95 percent confidence interval, 58.7 to 99.8), with a 2 percent false positive rate. Nine of the 11 cases of trisomy 18, including the single false negative case, were identified as positive for trisomy 21 on screening. Of the 2 percent of patients with positive screening results for trisomy 18, 34 percent also had positive

Table 2. Performance of First-Trimester Screening Tests for Trisomy 21, Trisomy 18, and Either Trisomy 21 or 18 in 8216 Pregnant Patients.*

Screening Test	No. of Patients	Trisomy 21 (N=61)				Trisomy 18 (N=11)		Trisomy 21 or 18 (N=72)	
		Detection Rate with Cutoff of 1:270	False Positive Rate with Cutoff of 1:270	Detection Rate with 5% False Positive Rate	Detection Rate with 1% False Positive Rate	Detection Rate with Cutoff of 1:150	False Positive Rate with Cutoff of 1:150	Detection Rate	False Positive
		percent (95 percent confidence interval)							
Maternal age alone	8216	80.3	48.0	32.8	9.8	27.3	7.2	77.8	48.0
Maternal age and serum biochemical measurements	8216	85.2	23.2	67.2	34.4	81.8	3.3	87.5	26.1
Maternal age and nuchal translucency	8216	82.0	11.9	68.8	47.5	81.8	2.9	81.9	11.8
Maternal age, serum biochemical measurements, and nuchal translucency	8216	85.2 (73.8–93.0)	9.4 (8.8–10.1)	78.7 (66.3–88.1)	63.9 (50.6–75.8)	90.9 (58.7–99.8)†	2.0 (1.7–2.3)	88.9 (79.3–95.1)	10.7 (10.1–11.4)
Maternal age <35 yr‡	4096	66.7 (34.9–90.1)	3.7 (3.2–4.3)	66.7 (34.9–90.1)§	50.0 (21.1–78.9)§	66.7 (9.4–99.2)	1.3 (1.0–1.7)	80.0 (51.9–95.7)	4.7 (4.1–5.4)
Maternal age ≥35 yr¶	4120	89.8 (77.8–96.6)	15.2 (14.1–16.3)	77.6 (63.4–88.2)§	67.4 (52.5–80.1)§	100 (63.1–100)	2.6 (2.2–3.2)	91.2 (80.7–97.1)	16.8 (15.7–18.0)

* Maternal age was the patient's age at the estimated date of delivery.
† The results exclude one patient with a positive screening test for trisomy 21. The inclusion of this patient would have resulted in a detection rate of 100 percent.
‡ Among these patients, 12 had a fetus with trisomy 21 and 3 had a fetus with trisomy 18.
§ The 5 percent and 1 percent false positive rates were calculated for the specific maternal age cohort.
¶ Among these patients, 49 had a fetus with trisomy 21 and 8 had a fetus with trisomy 18.

screening results for trisomy 21. As compared with screening for trisomy 21 alone, the addition of screening for trisomy 18 resulted in the detection of two additional cases of trisomy 18 and 1 additional case of trisomy 21, with an associated increase of 1.4 percent in the false positive rate. Coincidentally, four of five cases of trisomy 13 were identified; three were positive for both trisomies 21 and 18 on screening, and one was positive for trisomy 21 alone. Three of the four patients with triploid pregnancies had a positive screening result: one was at risk for having a fetus with trisomy 21, and two were at risk for having a fetus with trisomy 18.

Of the pregnancies involving trisomy 21, all 5 that were spontaneously aborted and all 15 that were electively terminated before week 15 were positive on screening, as were 20 of the 25 pregnancies terminated later in the second trimester and 12 of the 16 live-born infants. There was no significant difference in the results of screening between patients who had a spontaneous loss of pregnancy and those who delivered live-born infants (P=0.35).

We used ROC curves to evaluate the performance of the various approaches to screening (Fig. 2). There was a significant difference overall among the screening approaches (P=0.002). In pairwise tests, the combined screening test performed significantly better than evaluation with use of the biochemical component alone (P=0.006), but it was not significantly better than screening with use of the nuchal-translucency component alone (P=0.28). ROC curves showed no advantage for any particular sampling period between 74 and 97 days of gestation.

Table 3 presents the first-trimester screening results for the nine patients with false negative tests for trisomy 21. Seven of these patients underwent triple screening during the second trimester. The results were positive for six (85.7 percent) when the cutoff was 1:270. With the use of a second-trimester false positive rate of 5 percent (a cutoff value of 1:150), the results were positive for five of the seven patients (71.4 percent) with false negative first-trimester results. The use of a 1 percent rate of false positive second-trimester results (a cutoff value of 1:43) would still have identified four of the seven (57.1 percent).

DISCUSSION

We have demonstrated at multiple clinical sites in North America that screening for Down's syndrome

and trisomy 18 can be performed in a practical manner during the first trimester. Using a combination of maternal age, nuchal-translucency thickness, and levels of maternal serum analytes, we could identify 78.7 percent of fetuses with trisomy 21, with a false positive rate of 5 percent. This result is better than the detection rate of approximately 65 percent reported with the use of second-trimester triple-marker screening and is similar to the rate of 75 percent reported with the addition of inhibin A levels to second-trimester triple-marker screening (on the basis of a 5 percent false positive rate).[2]

Among women who were 35 years of age or older, many of whom may have elected to undergo screening to avoid an invasive procedure, all pregnancies involving trisomy 18 and 89.8 percent of those involving trisomy 21 were identified by screening, with a false positive rate of 15.2 percent. Thus, if screening results were used preferentially over maternal age, 85 percent of women 35 years of age or older could avoid an invasive procedure. At the same cutoff value of 1:270, the use of second-trimester triple-marker screening in women who are 35 years of age or older would identify a similar proportion of fetuses (89 percent) with trisomy 21 but with a false positive rate of 34 percent.[14]

Comparisons of the clinical performance of first- and second-trimester screening must take into consideration differences in the rates of spontaneously aborted pregnancies involving trisomy 21 at various gestational ages. We used the calculations suggested by Dunstan and Nix[15] and published information regarding the rates of spontaneous first- and second-trimester losses of pregnancies involving trisomy 21[16] to account for these differences. Since 69 percent of fetuses with trisomy 21 identified in the first trimester and 76 percent of those identified in the second trimester will be viable, second-trimester screening would have to detect 75 percent of fetuses with Down's syndrome to be considered similar to our first-trimester detection rate of 79 percent.

First-trimester screening would lose some advantage if it preferentially identified nonviable pregnancies involving trisomy 21. Using the above estimates of the gestational-age–dependent viability of pregnancies involving trisomy 21 and assuming the worst-case scenario — that all terminated pregnancies that were negative for trisomy 21 on screening would have resulted in a live birth — we estimated that at least 80 percent of the fetuses identified as having Down's syndrome would have been born alive. (see the Supplementary Appendix, available
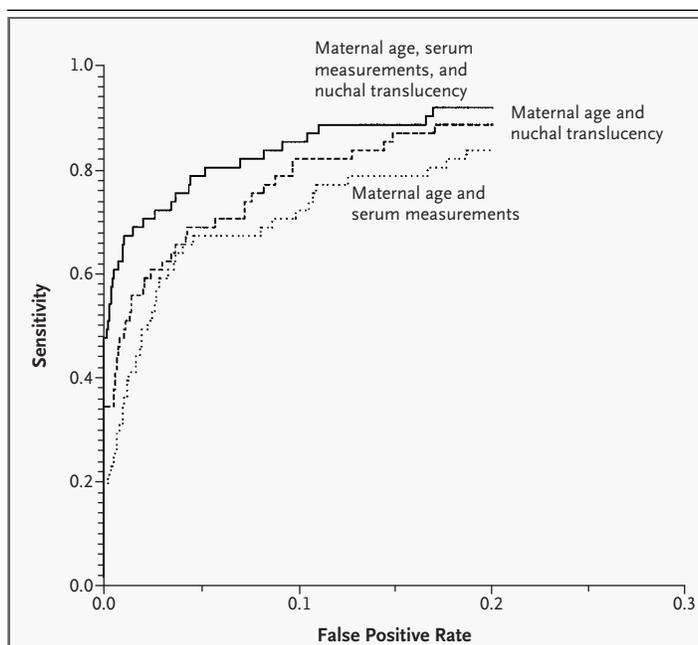

Figure 2. Receiver-Operating-Characteristic Curves for the Prediction of Trisomy 21 with Use of the Combined Approach to Screening, Screening Based on Maternal Age and Nuchal Translucency, and Screening Based on Maternal Age and Serum Measurements.

Table 3. Serum Biochemical and First-Trimester Nuchal-Translucency Values and Calculated Risk for the Nine Patients with a Fetus with Trisomy 21 and a Negative Result on First-Trimester Screening.

Maternal Age	Pregnancy-Associated Plasma Protein A	Free β Human Chorionic Gonadotropin	Nuchal Translucency	Risk of Trisomy 21*
yr	*multiples of the median*			
37	0.96	2.39	0.79	1:295
42	1.26	0.96	0.96	1:321
41	1.13	0.90	1.04	1:501
40	0.69	1.01	0.98	1:515
35	0.64	0.61	1.52	1:1392
33	0.83	1.12	1.18	1:1830
34	0.30	0.23	1.47	1:2037†
31	0.44	1.16	0.89	1:2283
33	0.73	0.80	1.14	1:3521

* The risk was based on maternal age, serum biochemical values, and nuchal-translucency measurements combined.
† Although the results of screening were negative for trisomy 21, they were positive for trisomy 18.

with the full text of this article at http://www.nejm.org). Thus, the good performance of first-trimester screening is not simply based on the identification of pregnancies that would have been spontaneously aborted anyway.

Concern has been expressed that standardization of nuchal-translucency measurements may not be feasible in clinical practice.[17] However, we used more than 40 sonographers at 12 centers and had excellent screening results. In our experience, a learning period was required, with measurements becoming more consistent over time. This required stringent training, formalized evaluation of sonographers' competence, and continuing external quality control.

A review of our false negative results for trisomy 21 reveals that the majority of the risk estimates were well below the 1:270 cutoff, with only one of the nine between 1:271 and 1:300. Seven had values of less than 1:500. This finding suggests that minor modifications of the methods will not substantially improve screening performance. Several other complementary approaches to first-trimester screening have been suggested, including the use of new ultrasonographic markers (for example, nasal-bone hypoplasia and ductus venosus Doppler flow),[18,19] sequential use of second-trimester biochemical analytes,[20] and analysis of fetal DNA or fetal cells in the maternal circulation.[21-23] The roles of these variables in screening will require formal evaluation.

The usefulness of second-trimester screening in a patient who had negative results during the first trimester is unclear. Of our nine patients with false negative results for trisomy 21, seven underwent second-trimester screening and six were found to be positive. Use of a 1 percent false positive rate for the second-trimester screening would have identified four of these seven patients. Although sequential first- and second-trimester screening may have some role, further detailed evaluation is required. This includes an understanding of the interaction of first- and second-trimester analytes and the balance among improved rates of detection, an increased false positive rate, the delay in informing patients of their risk, and the costs of this approach.

The 61 pregnancies involving trisomy 21 identified in our population exceeds the 49 predicted on the basis of maternal-age distribution. Women who were referred because of a finding of increased nuchal translucency were not included in this study; thus, ascertainment bias is unlikely. This observation, although difficult to explain, gives us confidence that our ascertainment of affected pregnancies was maximized.

In conclusion, our cohort study shows that first-trimester screening that combines maternal age, levels of pregnancy-associated plasma protein A and free β human chorionic gonadotropin, and nuchal-translucency thickness is accurate and efficient in clinical practice. Its performance is good as compared with second-trimester screening, even after adjustment for potentially nonviable pregnancies. Most important, first-trimester screening with these markers offers patients greater privacy, earlier results, and safer reproductive alternatives than second-trimester screening.

APPENDIX

In addition to the authors, the members of the First Trimester Maternal Serum Biochemistry and Ultrasound Fetal Nuchal Translucency Screening (BUN) Study are as follows: Drexel University College of Medicine — M. DiVito, M. McGee, E. Waters, and P. Morgan; Baylor College of Medicine — J. Dungan, K. Leonard, N. Agan, and G. Brewster; Northwestern University Medical School — N.A. Ginsberg and K. DeMarco; Evanston Hospital of Northwestern University Medical School — K. Blum, E. Leeth, M. Kambick, L. Geibel, and P. Chilis; Cedars–Sinai Medical Center — D.E. Carlson and C.A. Walla; Magee Women's Hospital: E. Smith, K. Ventura, and J. Hecker; UCLA Center for the Health Sciences — S. Beverly; Wayne State University — M.C. Treadwell, E. Krivchenia, P. Devers, and R. Richter; Yale University — R. Bahado-Singh, S. Turk, and M. Feather; McMaster University Medical Centre — M.L. Beecroft and S. Kinnear; BC Women's Hospital — S. Soanes and A. Sleep; Prenatal Diagnosis of Northern California Medical Group — K. Kahl and M. Palmer; George Washington University Biostatistics Center — P. Van and B. Fisher; and the National Institute of Child Health and Human Development — F. de la Cruz.

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