



Clinical use of first-trimester aneuploidy screening in a United States population can replicate data from clinical trials

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KEY WORDS

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Objective: The clinical application of first-trimester aneuploidy screening remains controversial in the United States. The aim of our study was to evaluate the performance of maternal age, fetal nuchal translucency measurements, pregnancy-associated plasma protein A, and free beta-human chorionic gonadotrophin used in aneuploidy screening in a single institution outside of a clinical trial.

Study design: Four thousand eight hundred eighty three patients underwent first-trimester aneuploidy screening at 11 to 13 6/7 weeks of gestation (fetal crown-rump length 45 mm to 84 mm) at our institution between January 2003 and September 2004. Measurement of nuchal translucency was performed according to the Fetal Medicine Foundation standards and was included in the overall risk assessment performed by NTD Laboratories. Measurement of pregnancy-associated plasma protein A and free beta-human chorionic gonadotrophin on maternal dried whole blood samples was conducted by NTD Laboratories and was reported as gestational-specific multiples of the median adjusted for ethnicity. Risk adjustment for trisomy 21 and trisomy 18 was done with a standard algorithm using maternal age, serum biochemistry, and nuchal translucency. Only singleton gestations (N = 4615) were included in the analysis.

Results: The median maternal age was 33.0 years (interquartile range 31.0 to 36.0) and the median crown-rump length was 61.2 mm (interquartile range 55.7 to 67.2) at the time of screening. There were a total of 22 fetuses diagnosed with trisomy 21 and 8 with trisomy 18. The detection rates for trisomy 21 for a 5% false-positive rate and 1% false-positive rate were 90.9% (20 of 22) and 77.3% (17 of 22), respectively. Similarly, the detection rates for trisomy 18 at a 5% false-positive rate and a 1% false-positive rate were 100% (8 of 8) and 100% (8 of 8), respectively.

Conclusion: Non-investigational use of first-trimester aneuploidy screening for trisomy 21 and trisomy 18 can replicate results from investigational trials.

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Prenatal diagnosis of fetal aneuploidy requires invasive procedures such as amniocentesis and chorionic villus sampling.¹ Although complications are uncommon, both procedures are associated with an increased risk of pregnancy loss.^{2,3} In the United States, most procedures are performed because of maternal age of 35 years or older, although the use of age as the only screening modality does not lead to the detection of most affected fetuses.⁴

The use of multiple marker biochemical screening for fetal aneuploidy in the second trimester has become widespread.^{4,5} In women under the age of 35 years, these tests can identify the majority of pregnancies with trisomy 21 and trisomy 18 with low false-positive rates. The results of these tests can also modify risk estimates and are often used to assist women in deciding whether to undergo amniocentesis.⁶

First-trimester risk assessment for Down syndrome, which can lead to an earlier diagnosis, is available.⁷⁻¹⁰ Nuchal translucency, the sonographic measurement of posterior nuchal skin, combined with maternal age has a sensitivity of approximately 80%, with a false-positive rate of 5%.¹ When nuchal translucency is combined with first-trimester serum screening and maternal age, sensitivity may be as high as 90%, with a false-positive rate of 5%.⁹ Proper training of sonographers and quality assurance programs are fundamentally important in achieving high sensitivities in first-trimester aneuploidy risk assessment at acceptable false-positive rates. However, not all studies have verified such a high sensitivity.¹¹ The largest studies evaluating first-trimester screening in the United States have come from 2 prospective, multicenter studies sponsored by the National Institute of Child Health and Human Development.^{8,12}

Although both these studies have described high detection rates for first-trimester combined risk assessment, some have cautioned against the implementation of first-trimester screening in the United States.¹³ Concerns have included the ability to accurately measure nuchal translucency and the cost and feasibility of screening large populations of women. If the performance of first-trimester screening in non-investigational settings cannot replicate results seen in clinical trials, widespread implementation may not be appropriate.

In our unit we have offered first-trimester screening under the auspices of the Fetal Medicine Foundation (FMF), which standardized nuchal translucency measurement and algorithms for risk assessment since 2000. Our data on the use of risk assessment using maternal age and nuchal translucency were consistent with many centers using identical techniques.¹⁴ Since 2003 we have estimated risk using maternal age, nuchal translucency, and biochemistry. The 2 prospective National Institutes of Health-funded trials (ie, First Trimester Maternal Serum Biochemistry and Ultrasound Fetal Nuchal

Translucency Screening Study [BUN] and First- And Second Trimester Evaluation of Risk of Aneuploidy Study [FASTER]) on aneuploidy risk assessment were conducted at specially selected tertiary care referral centers with the implementation of strict quality-control measures.^{8,12} The objective of our study was to assess the performance of first-trimester combined screening in a non-investigational setting in a single institution in an American population under circumstances available at any institution in the United States.

Material and methods

First-trimester combined screening data from patients with singleton pregnancies who presented from January 2003 through September 2004 in the New York Weill-Cornell Medical Center were reviewed. Screening for trisomies 21 and 18 was performed between 11 0/7 and 13 6/7 weeks (crown-rump length [CRL] 45 to 84 mm). Risk assessment was performed using maternal age, nuchal translucency (NT) measurement, and levels of the maternal serum analytes, pregnancy-associated plasma protein A (PAPP-A) and free beta-human chorionic gonadotrophin (β hCG).

Ultrasonographic measurement of fetal NT was performed by 1 of 14 registered diagnostic medical sonographers at our institution according to established standards of the FMF (London, United Kingdom).¹ NT measurements were periodically monitored for quality assurance by comparing values obtained at our center with norms established by the FMF. Ultrasound images were obtained with a 6-MHz transabdominal transducer, with multihertz and harmonic capability (Sequoia system 512; Acuson, Mountain View, CA).

Blood was obtained from each patient for serum biochemical analysis (PAPP-A and free β -hCG) with application of 5 spots on standard filter paper after the NT measurement was completed. The dried blood sample along with the NT measurement was subsequently sent to NTD Laboratories (Huntington Station, NY) for analysis within 24 hours. The specimens were appropriately prepared and analyzed by methodology previously described elsewhere.^{8,15,16} Gestational age-specific multiples of the median were generated for the serum analytes and adjusted for maternal ethnicity and delta-NTs were calculated. These were converted into likelihood ratios derived from previous studies.^{1,15}

Maternal demographic factors were collected at the time of first-trimester screening enrollment. Fetal chromosomal status was determined by prenatal karyotype analysis if chorionic villus sampling or amniocentesis was performed, cytogenetic studies on tissue in the case of spontaneous loss or stillbirth, or phenotypic evaluation after delivery by the attending pediatrician. Outcome variables were retrieved from computerized medical record review.

Table Maternal and fetal demographic characteristics of trisomy 21, trisomy 18, and euploid singleton pregnancies

	Trisomy 21 (N = 22)	Trisomy 18 (N = 8)	Euploid (N = 4578)
Median maternal age, yr (interquartile range)	38.0 (36.0-40.0)	37.5 (32.2-39.0)	33.0 (31.0-36.0)
Median maternal weight, lb (interquartile range)	141.0 (128.8-156.8)	120.0 (110.3-158.5)	135.0 (122.0-150.0)
Median fetal CRL, mm (interquartile range)	61.4 (53.0-65.5)	53.1 (48.3-54.3)	61.2 (55.8-67.3)
Median fetal NT, mm (interquartile range)	2.8 (1.9-3.6)	5.1 (2.3-5.6)	1.5 (1.3-1.8)
Median free β hCG MOM (interquartile range)	1.93 (1.69-2.86)	0.28 (0.18-0.65)	0.96 (0.67-1.35)
Median PAPP-A (interquartile range)	0.57 (0.34-0.94)	0.21 (0.13-0.23)	1.2 (0.81-1.74)

MOM, Multiples of the median.

The detection rates for trisomies 21 and 18 were calculated for a fixed 5% and 1% false-positive rate (FPR). Statistical analysis was performed with the use of the Statistical Package for the Social Sciences software (SPSS release 11.0; SPSS Inc., Chicago, IL). A probability value less than 0.05 was considered statistically significant. The study was approved by the Committee for Human Rights in Research/Institutional Review Board at the Weill Medical College of Cornell University.

Results

A total of 4883 pregnant women carrying 5166 fetuses underwent first-trimester risk assessment for aneuploidy between January 2003 and September 2004. There were 268 multifetal pregnancies (253 twin pregnancies and 15 triplet pregnancies) excluded. The remaining 4615 pregnancies were included.

The median maternal age at the estimated date of confinement was 33.0 years (interquartile range of 31.0 to 36.0). The median maternal weight at the time of blood sample collection was 135.0 pounds (interquartile range 122.0 to 150.0). The maternal ethnic distribution was the following: 73.1% white, 8.4% Asian, 8.4% Hispanic, 4.8% African American, 3.4% other, 1.5% Asian Indian, and 0.4% Native American. The distribution of gestational age week intervals at patient presentation for aneuploidy screening was the following: 18.7% at week 11, 60.2% at week 12, and 21.1% at week 13.

The median fetal CRL measurement at the time of the first-trimester screening was 61.2 mm (interquartile range 55.7 to 67.2). The median fetal NT measurement was 1.6 mm (interquartile range 1.3 to 1.8).

The characteristics of the trisomy 21, trisomy 18, and euploid gestations are shown in the [Table](#).

There were a total of 37 aneuploid fetuses in our patients: 1 with trisomy 13 (2.7%), 8 with trisomy 18 (21.6%), 22 with trisomy 21 (59.5%), 4 with 45X (10.8%), 1 with 47XXY (2.7%), and 1 with triploidy (2.7%).

The NT (CRL) measurements for each of the fetuses with trisomy 13, 47XXY, and triploidy are as follows: 1.7 mm (54 mm), 2.2 mm (65 mm), and 1.3 mm (51 mm), respectively. The median NT (interquartile range) and CRL (interquartile range) measurements for the four

45X fetuses are 7.3 mm (3.0 to 9.0) and 61.9 mm (60.0 to 63.9), respectively.

There were 22 cases of trisomy 21 (prevalence 1 in 210) and 8 cases of trisomy 18 (prevalence 1 in 577). Of the 22 cases of trisomy 21, 3 (13.6%) resulted in a live birth and 19 (86.4%) were electively terminated. There were no spontaneous losses, although most affected pregnancies (19 of 22, 86.4%) were electively terminated following prenatal diagnosis. Of the 22 pregnancies with trisomy 21, 19 (86.4%) were in women who were 35 years or older at the estimated date of confinement. All 8 fetuses with trisomy 18 were electively terminated. Of the 8 fetuses with trisomy 18, 6 (75%) were in women who were 35 years or older at the estimated date of confinement.

The sensitivities for trisomy 21 detection for a 5% (1 in 269) FPR and a 1% (1 in 40) FPR were 90.9% (20 of 22) and 77.3% (17 of 22), respectively. Similarly, the sensitivities for trisomy 18 detection for a 5% (1 in 2154) FPR and a 1% (1 in 201) FPR were 100% (8 of 8) and 100% (8 of 8), respectively.

In the 22 pregnancies with a trisomy 21 fetus, the median factor of risk adjustment (adjusted risk/age-related risk) was 15.0 (interquartile range 2.4 to 31.6). The adjusted risk was higher than the age-related risk in 18 cases (81.8%) and lower than the age-related risk in only 4 cases (18.2%). In pregnancies with a euploid fetus, the median factor of risk adjustment was 0.10 (interquartile range 0.10 to 0.10).

Comment

It has previously been demonstrated that first-trimester screening for fetal aneuploidy can be performed successfully in large, multicenter clinical trials.^{1,8,12} Our study shows that screening programs for trisomies 21 and 18 based on maternal age, fetal NT measurement, and the serum markers PAPP-A and free β -hCG can be effectively implemented into clinical practice. Our detection rate is consistent with the 90% detection rate of trisomy 21 and 100% detection rate for trisomy 18 for a fixed 5% FPR described by those using similar techniques for risk assessment.⁸⁻¹⁰

Our population, with a median maternal age of 33 years and 25% of patients 36 years or older, is older

than the general obstetric population in the United States. Because maternal age is incorporated in risk assessment, one could speculate that our high detection rate might be due to high a priori risk. In fact, most pregnancies with a Down syndrome fetus had adjusted risks that were substantially higher than age-related risks. The detection rate at our 5% false-positive cutoff of 1 in 269 is also very close to the risk of a 35-year-old woman, the commonly accepted threshold for offering invasive procedures.

Our successful implementation of first-trimester risk assessment relied on our strict adherence to the guidelines set forth by the FMF. The importance of this has been demonstrated by Monni et al,¹⁷ who observed an increase in their detection rate of trisomy 21 from 30% to 84% after modifying their technique of NT measurement.⁹ Because the risk assessment algorithm treats the NT measurement like a laboratory analyte, the precision in measuring NT should be equivalent. With appropriate training and ongoing quality assurance, similar medians and distributions of NT measurements based on gestational age have been described in many different populations.¹⁸

Although the performance of first-trimester risk assessment in our unit was consistent with that of clinical trials, our results are not necessarily widely applicable. Our obstetric ultrasound unit has highly trained sonographers and physicians. We have been measuring NT since 2000, and our ability to accurately measure NT has come with great experience. The laboratory measuring biochemical analytes has a large amount of experience, and the analytes measured are those associated with the highest screening performance.¹⁹ It may not be reasonable to expect similar performance in units less experienced at measuring NT or with laboratories using different analytes.

In summary, first-trimester risk assessment for fetal aneuploidy on the basis of maternal age, NT measurement, and maternal levels of PAPP-A and free β -hCG have demonstrated high sensitivity with low FPRs in clinical trials. Our study clearly shows that non-investigational use of first-trimester aneuploidy screening for trisomies 21 and 18 in a United States population can replicate results from investigational trials when appropriate techniques are employed.

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