First-trimester combined screening: experience with an instant results approach

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OBJECTIVE: This study was undertaken to assess an instant results protocol for first-trimester combined screening.

STUDY DESIGN: Retrospective analysis of patients having first-trimester combined screening between Nov. 1, 2003 and Oct. 31, 2005. We evaluated the feasibility of patient self-collection and mail-in of blood samples before nuchal translucency ultrasound. Primary outcome was success with providing in-office, immediate screening results after the ultrasound. Predictor variables included age, ethnicity, insurance, and provider. The χ^2 analysis was performed.

RESULTS: Two thousand three hundred ten women completed first-trimester combined screening, and 60.6% received instant results. When the biochemistry sample was collected at home, 80% received instant results. Age 35 years or older predicted instant results ($P = .001$), whereas ethnicity, insurance, and referring provider did not. Comparing the prior 24 months, clinic volume increased by 18%. Diagnostic procedure volume was unchanged, although chorionic villus sampling increased by 12% ($P = .02$) and amniocentesis decreased by 6% ($P = .049$).

CONCLUSION: Patients were able to obtain instant results in 60.6% of cases, which appeared to increase the use of chorionic villus sampling.

Key words: Down syndrome screening, first-trimester combined screening, nuchal translucency, prenatal diagnosis

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Two large recent US studies have demonstrated the efficacy of first-trimester combined screening (FTCS) for chromosomal abnormalities in the fetus.[1,2] First-trimester screening provides 2 primary benefits when compared with second-trimester screening: earlier results and improved detection rate. Earlier results allow a decreased period of anxiety for patients, as well as the provision of first-trimester diagnostic testing for those found to be at increased risk. For those patients with confirmed abnormal karyotype who do decide to terminate their pregnancies, first-trimester abortion is safer and more readily available in most regions. It also appears to be more acceptable to women.[3]

The University of California, San Francisco (UCSF) Prenatal Diagnostic Center began offering nuchal translucency screening in 1998. After publication of the Serum Urine and Ultrasound Screening Study (SURUSS) in Europe[4] and the BUN study in October 2003,[1] it was clear that adding biochemistry to nuchal translucency (NT) ultrasound greatly improved detection rates and decreased false-positive rates for patients requesting early screening. We considered how best to introduce this component of screening into our practice. Challenges included obtaining the blood in the appropriate, relatively narrow gestational age window, assuring the NT ultrasound was scheduled in the appropriate time frame, determining how best to convey results to the patient, assuring first-trimester diagnostic testing, chorionic villus sampling (CVS), was available to as many patients as possible (including the many patients who travel long distances to our referral practice), and assuring that patients understood the nature of the test. Given that the test was new and not yet considered standard of care during the period of this study, pretest and posttest explanation of first- vs second-trimester screening were important considerations particularly for women younger than 35 years.

We instituted an instant results protocol for provision of FTCS in November 2003. This protocol involved patient blood collection at home by using a finger stick and filter paper mail-in card, before NT ultrasound. Biochemistry results were combined with the NT results on the day of the ultrasound appointment, and provided to the patient immediately after completion of the NT measurement. Patients with abnormal results were offered immediate CVS or diagnostic testing with CVS or amniocentesis at a later date.

We wished to review the outcomes of the first 2 years of our instant results protocol. In particular, we were interested in how many first-trimester screens could be completed at the time of ultrasound and what patient characteristics predicted completion in a timely fashion.

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Materials and Methods

This study is a retrospective cohort study of all patients seen in our office for first-trimester screening from Nov. 1, 2003, through Oct. 31, 2005. Before that time, our program had offered NT ultrasound only. Beginning in November 2003, all patients calling our office to request first-trimester screening were offered combined screening with NT and biochemistry (pregnancy-associated plasma protein [PAPP-A] and free beta hCG). Biochemical testing for PAPP-A and free beta hCG was available through NTD Laboratories (New York, NY) using a finger stick and filter paper mail-in card. Patients who called requesting FTCS were mailed a kit to collect blood for biochemical screening, and would then mail the filter paper mail-in card with the blood sample directly to the laboratory. They were also scheduled for an NT ultrasound in the appropriate time frame, ideally at least 1 week later than the blood was obtained to assure that biochemical results would be available. Instructions for collecting the blood sample were explained by phone. Written instructions were also mailed with the sample collection kit, including information regarding dates during which a valid blood sample could be obtained. Patients who were unable or unwilling to collect the blood sample at home could alternatively have a blood sample obtained in our office the day of the NT ultrasound appointment or could be seen in our office or their referring provider's office for assistance with blood collection before their NT appointment.

During their office appointment, patients who were age 35 years and older met with a genetic counselor for a formal genetic counseling session. In addition to standard information provided in such a counseling session, the first-trimester screening test was reviewed, including benefits, limitations, and comparison with other available prenatal testing options. The patient then underwent ultrasound for NT measurement by a certified provider. NT measurements were obtained in the standard fashion as described in the Fetal Medicine Foundation protocol.[5]

Results of that ultrasound (NT and crown rump length) were then immediately combined with biochemical results via direct computer access (password protected) to the laboratory. Combined results were provided to the patient by a genetic counselor before the patient left our office. Limitations of screening were again reviewed, and options for further screening or for diagnostic testing were discussed. In patients who were screen positive, same-day CVS was provided when possible (not all providers perform CVS so this was not always an option). CVS or amniocentesis at a later date were also offered as options.

We evaluated our program by determining the percentage of patients who were able to complete blood screening in a time frame allowing them to receive instant results in our office at the time of the NT ultrasound. Secondary outcomes included combined screening vs single screening (eg, providing results based on NT or biochemistry only). Predictor variables evaluated included age, ethnicity, insurance status, and referring provider. In addition, we conducted a historical control study of all patients seen in the Prenatal Diagnostic Center over a 4-year period from November 2001-October 2005 to determine changes in our overall volume of patients, and changes in volume of diagnostic procedures.

Categorical outcomes were examined with the χ^2 test. Statistical significance was determined by a P-value $<.05$. The study was performed with approval of the UCSF Committee on Human Research.

Results

During the 2-year study period, 2806 women were seen for first-trimester screening.

In the total group, 2444 women requested FTCS, whereas 362 declined biochemistry and requested NT only. Patients with Medicaid insurance coverage were more likely to request NT only, as opposed to combined screening (72% vs 28%, $P = .001$).

In women who requested FTCS and presented to our office for NT ultrasound, 69 (2.8%) were found to have a nonviable pregnancy, 16 (0.6%) women declined further screening after genetic counseling, 18 (0.8%) were found to be too advanced in gestation for NT ultrasound and received results based on the previously collected biochemistry sample, and 31 (1.2%) received NT results only for any of the following reasons: the blood sample was insufficient or lost in the mail and redraw was declined or the gestational age was too advanced, or a twin demise was diagnosed on the ultrasound. The remaining 2310 (94%) received a combined result (Figure). In all, 58% were aged 35 years or older (Table 1). With regard to ethnic background, 69% were white, 18% were Asian, 4.8% were Hispanic, 1.6% were African American, and the remaining 1.1% were of other ethnicities (Table 2). The majority (87%) had private insurance.

In the 2310 women who received FTCS results, 1400 (60.6%) received instant results, whereas 910 received their results at a later date. Reasons for not receiving instant results included collecting the blood sample at a time too close to the NT appointment, providing an insufficient sample that required repeat collection, or requiring assistance with obtaining the sample. Only age 35 years or older predicted greater likelihood of receiving instant results ($P = .001$), whereas ethnicity and referring provider did not (Table 1).

In an analysis of patients who did not receive instant results, 357 (15.4%) had biochemical screening performed before the appointment but received results on a different day (performed too close to appointment, insufficient sampling, need of assistance), 507 (21.9%) performed biochemical screening at the time of the NT appointment and received results at a later date, and 46 (2.0%) had biochemical screening performed at a date later than the NT appointment with combined results received subsequently. Of the 1757 women who collected and mailed their biochemistry sample before their NT appointment, 1400, or 80%, received an instant result.

TABLE 1
Percentage of women receiving instant results by maternal age

Maternal age	Instant result	Later result	Total
≥35 y	846 (63.4%)*	488 (36.6%)	1334
<35 y	554 (56.8%)	422 (43.2%)	976
	1400 (60.6%)	910 (39.4%)	2310

* $P = .001$ for age ≥35 vs <35 y.

We also compared the overall volume of patients seen in the clinic over the 2 years of the study. Compared with the preceding 24 months, the overall clinic volume increased by 18%. Total diagnostic procedure volume did not change, although CVS increased by 12% ($P = .02$) and amniocentesis decreased by 6% ($P = .049$) (Table 3). In the time frame evaluated in this study, 10.2% of CVS procedures were performed after FTCS. This compares with 6.2% of CVS procedures being performed after NT ultrasound in the preceding 24 months. Of the additional volume of procedures performed, 42% were performed because of increased risk identified by FTCS.

Comment

FTCS is an effective screening test for Down syndrome and other chromosome abnormalities, with improved performance characteristics when compared with second-trimester triple or quad screening.[1,2,4] As information about this screening test is disseminated, an increasing number of obstetricians are likely to routinely offer FTCS to women of all ages. In turn, an increasing number of women are likely to avail themselves of earlier testing with improved detection rates. As awareness of this screening tool becomes more widespread, efficient and effective programs for provision of this service will become increasingly important.

The program that we developed resulted in provision of first-trimester combined results to 94% of patients. Instant results were provided to 60.6% of women, with a somewhat greater likelihood of receiving instant results in women 35 years of age or older. This may be due to increased motivation by older women to complete the blood testing in a timely fashion and receive their results as soon as possible. It is likely that the increased awareness of the potential of a chromosome problem in this population resulted in a heightened desire to receive results as quickly as possible. It is also likely that many of these women wished to maintain the option of CVS at the time of their NT ultrasound, and wanted complete information and results before making that decision.

Of the women who collected their biochemistry sample before the NT appointment, 80% were able to receive an instant result. In the women who had not completed prior biochemistry and thus were not expecting an instant result, many were unable to obtain the sample by themselves at home and requested assistance at the time of their appointment. It is likely that an approach whereby women have the option of assistance with obtaining the sample will eventually result in a higher overall ability to provide instant results, closer to the 80% observed in women who were able to collect the biochemical sample earlier.

TABLE 2
Percentage of women receiving instant results by ethnic background

Ethnicity	Instant result	Later result	Total
African-American	23 (51.1%)	22 (48.9%)	45
White	986 (61.9%)	607 (38.1%)	1593
Asian	294 (58.1%)	212 (41.9%)	506
Hispanic	80 (58.8%)	56 (41.2%)	136
Other/unknown	17 (56.7%)	13 (43.3%)	30
Total	1400	910	2310

Differences not significant between ethnic groups ($P = .2291$).

It is often discussed that women vary in their approach to prenatal diagnosis and screening on the basis of race or ethnicity. This was not found to be the case in our study, although the numbers are small, and those patients choosing to avail themselves of this still novel test are a select group. Recent literature indicates differences in prenatal test uptake amongst women of different ethnicities are mediated by many factors, including the failure to facilitate informed choice,[6] acculturation and language skills,[7,8] risk perception, attitudes toward abortion and health care systems in general, and values such as fatalism.[9] As some of these newer screening strategies are introduced into general practice, it is important that providers and policy makers consider women's preferences in establishment of screening programs.

Of interest was the lower rate of use of the biochemical component of FTCS by women with Medicaid coverage. We hypothesize that the primary reason for this was both the lack of insurance coverage for the biochemical screening as well as the likely lower incomes in this group. From a societal perspective, FTCS has been demonstrated to be cost-effective,[10,11] thus it behooves us to assure complete access to such testing to women from all sectors of our society. As we proceed with programmatic design and facilitation of coverage of such screening by both private and governmental insurance plans, such considerations should be taken into account.

Provision of instant results by a genetic counselor is of benefit for a number of reasons, including assuring that the patients have all questions answered regarding the test results, discussion of the limitations and further testing options, and the ability to discuss diagnostic testing for patients who wish to obtain a de-

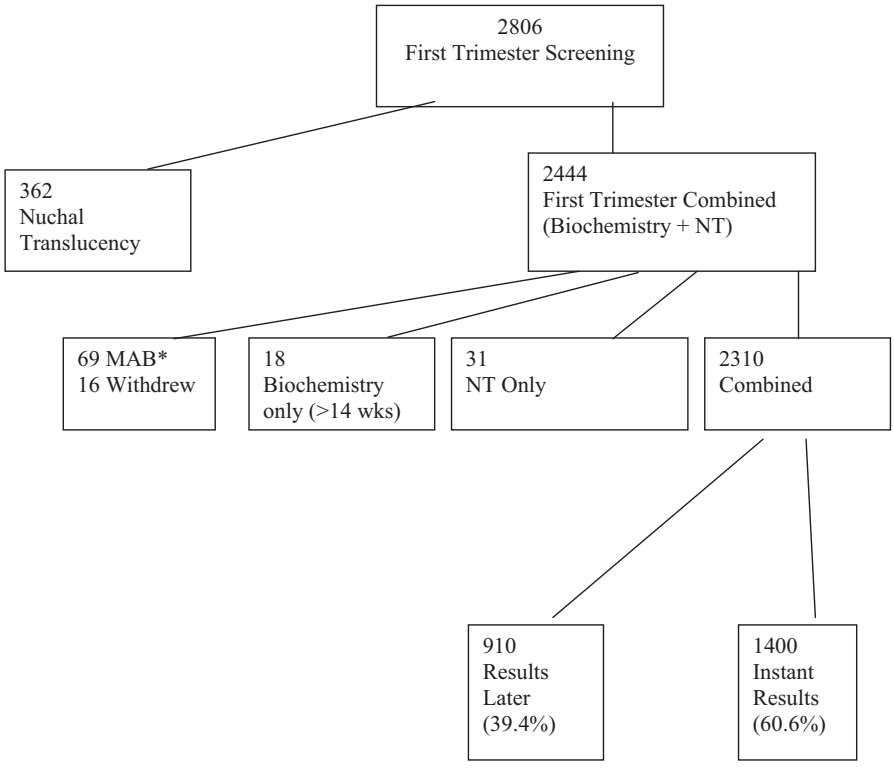
finitive result. In evaluating the obstacles to obtaining blood such that instant results were available, nearly 15% of patients sent the blood sample before their appointment, but not far enough in advance that results were available. One obstacle was the mail process itself, and we are considering a routine overnight shipping protocol to optimize timely receipt of the blood samples. This is likely to improve the number of women who are able to obtain instant results.

Another challenge to implementation of first-trimester screening programs is the increased demand for CVS that will likely occur. In fact, we noted a significant increase in our CVS volume (12%), largely because of the increased demand by women with positive screening results. A decrease in amniocentesis volume was noted as well, as most women who were screen negative declined diagnostic testing. Clinic volume is determined by many factors, including changes in birth rates, referral patterns, and insurance contracts, so it is difficult to draw conclusions regarding the overall clinic volume in this study. However, the difference in the ratio of CVS to amniocentesis is likely to be reflected in other programs as FTCS becomes more widespread. Consequently, more providers trained in CVS will be required.

Although our study presents an assessment of one approach to the provision of FTCS, it is not without limitations. Because of its retrospective nature, we were unable to directly interview the women as they were going through their decisions. To accurately determine how women choose their testing strategy, and examine the reasoning behind such choices, requires prospective evaluation with direct interaction with the individual women. Such evaluation is important as policy makers struggle with decisions as to which tests will be offered, recommended, and covered by insurance providers. In addition, we lacked some information on the women with respect to income and education level that may predict both choice of and success in using the program to achieve instant results. As a retrospective cohort study, there may be potential confounders for maternal age that we did not identify. Of those that we examined, insurance status and race/ethnicity, there was no association with the rate of instant results. Because these variables were not confounders, multivariate analysis was not conducted. However, others for which we did not have data may have existed.

Despite these limitations, we believe that our overall results are very promising. As the NT component of FTCS will be limited to referral centers in the foreseeable future, being able to provide complete information during a patient's visit is paramount. It appears that such provision of complete information is achievable. ■

FIGURE
Flow diagram illustrating results of first-trimester screening program



*MAB = missed abortion.

TABLE 3
Patient volume and procedures 24 months prior vs first 24 months' combined program

	Nov. 1, 2001-Oct. 31, 2003	Nov. 1, 2003-Oct. 31, 2005	
CVS*	759 (28%)	852 (31%)	$P = .003$
Amniocentesis	1982 (72%)	1860 (69%)	
Total procedures	2741	2712	
Total patient volume	7047	8343	

* CVS as proportion of total procedures.

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Discussion

David C. Lagrew Jr, MD. Congratulations to Dr Norton et al for sharing their excellent results and analysis of an important application of the new technique of screening women for genetic screening for aneuploidy in pregnant women. Specifically, the report describes the effectiveness and outcomes of introducing "Instant Results" of first-trimester combined ultrasound/serum screening. Studies such as this are important because genetic screening techniques are rapidly becoming the preferred method of care in many areas, despite the lack of careful analysis of the "application" of the technology with respect to the functionality, efficiency, acceptance, and impact compared with other services.

First trimester screening techniques were first introduced by Nicholides et al in England in the early 1990s. They found that the combination of measuring the fetal nuchal lucency combined with serum estriol and human chorionic gonadotropin was effective in assessing risk for trisomy 21 and 18 between the 11th and 13th weeks of pregnancy.[1] The obvious benefit of obtaining earlier results in pregnancy was augmented with an improvement in the sensitivity and specificity compared with second-trimester serum screening. Earlier results also opened up the options of CVS and earlier amniocentesis while giving the mother more time to carefully evaluate the results and the possibility of termination in a safe and psychologically desirable period.

Adoption of the technique in the United States rapidly followed based on large trials, such as the BUN trial,[2] noted by Dr Norton. In addition to requiring strict quality control of ultrasound and serum testing, first-trimester screening involves revamping our current methods of reporting results to patients and the recommendation of other noninvasive screening methods such as second-trimester screening and genetic ultrasound. The complexity of such goals and effects on patients is the subject of the current article. A specific focus of the report was to determine the value in obtaining serum screening before NT testing by ultrasound such that the patient could get immediate counseling and start the process regarding further definitive testing and other options.

Dr. Norton and colleagues retrospectively reviewed screening efforts on 2444 patients of which 58% were at or older than age 35. They were able to perform first-trimester screening in 94% of these patients and nearly two thirds (60.6%) were able to get results during their ultrasound visit. The authors found that maternal age was the only factor significantly correlated with success in obtaining instant results. Expeditious counseling was associated with a 12% rise in CVS procedures and a 6% decrease in the numbers of amniocenteses.

The results of the study are straightforward and logical. Patient's compliance and reliability are highly correlated to successful applications of patient care. In this study, patients who were more motivated to comply were able to receive their results in a timely fashion. This is an important lesson for all researchers to remember when designing clinical trials, because no method of testing will be successful when patient compliance is low. The common sense principal of "keep it simple, stupid" is too often forgotten by well meaning investigators who wish to squeeze out slight gains in sensitivity and specificity.

I encourage the authors to continue reporting their results in this dynamic area of outpatient care.

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