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First Trimester Combined Screening: Experience with an Instant Results Approach

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Abstract

Objective: To assess an instant results protocol for first trimester combined screening (FTCS).

Study Design: Retrospective analysis of patients having FTCS between 11/1/03 - 10/31/05. We evaluated the feasibility of patient self-collection and mail-in of blood samples prior to nuchal translucency ultrasound. Primary outcome was success with providing in office, immediate screening results following the ultrasound. Predictor variables included age, ethnicity, insurance, and provider. Chi-square analysis was performed.

Results: 2310 women completed FTCS, and 60.6% received instant results. When the biochemistry sample was collected at home, 80% received instant results. Age ≥ 35 predicted instant results ($p=0.001$), while ethnicity, insurance, and referring provider did not. Comparing the prior 24 months, clinic volume increased by 18%. Diagnostic procedure volume was unchanged, although CVS increased by 12% ($p=0.02$) and amniocentesis decreased by 6% ($p=0.049$).

Conclusion: Patients were able to obtain instant results in 60.6% of cases, which appeared to increase the utilization of CVS.

Keywords

first trimester combined screening; nuchal translucency; Down syndrome screening; prenatal diagnosis

Introduction

Two large recent U.S. studies have demonstrated the efficacy of first trimester combined screening (FTCS) for chromosomal abnormalities in the fetus^{1,2}. First trimester screening provides two primary benefits when compared to 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

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pregnancies, first trimester abortion is safer, and more readily available in most regions. It also appears to be more acceptable to women³.

The UCSF Prenatal Diagnostic Center began offering nuchal translucency screening in 1998. Following publication of the Serum Urine and Ultrasound Screening Study (SURUSS) in Europe⁴ and the BUN study in October 2003¹, it was clear that adding biochemistry to nuchal translucency 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 (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 time period of this study, pre- and post-test explanation of first versus second trimester screening were important considerations particularly for women less than 35 years of age.

We instituted an instant results protocol for provision of FTCS in November 2003. This protocol involved patient blood collection at home using a finger stick and filter paper mail-in card, prior to NT ultrasound. Biochemistry results were combined with the NT results on the day of the ultrasound appointment, and provided to the patient immediately following 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.

Materials and Methods

This study is a retrospective cohort study of all patients seen in our office for first trimester screening from November 1, 2003 through October 31, 2005. Prior to that time, our program had offered nuchal translucency ultrasound only. Beginning in November 2003, all patients calling our office to request first trimester screening were offered combined screening with NT and biochemistry (PAPP-A and free beta hCG). Biochemical testing for PAPP-A and free beta hCG was available through NTD Laboratories (New York, NY) utilizing a finger stick and filter paper mail-in card. Patients who called requesting first trimester combined screening 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 one 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 prior to their NT appointment.

During their office appointment, patients aged 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 to other available prenatal testing options. The patient then

underwent ultrasound for nuchal translucency measurement by a certified provider. Nuchal translucency measurements were obtained in the standard fashion as described in the Fetal Medicine Foundation protocol⁵.

Results of that ultrasound (nuchal translucency 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 prior to the patient leaving 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 versus single screening (e.g. providing results based on nuchal translucency or biochemistry only). Predictor variables evaluated included age, ethnicity, insurance status, and referring provider. Additionally, we conducted a historical control study of all patients seen in the Prenatal Diagnostic Center over a four-year period from November, 2001 to October, 2005 in order to determine changes in our overall volume of patients, and changes in volume of diagnostic procedures.

Categorical outcomes were examined with the chi-square test. Statistical significance was determined by a p-value<0.05. The study was performed with approval of the UCSF Committee on Human Research.

Results

During the two-year study period, 2806 women were seen for first trimester screening. In the total group, 2444 women requested combined screening, while 362 declined biochemistry and requested nuchal translucency only. Patients with Medicaid insurance coverage were more likely to request NT only, as opposed to combined screening (72% vs 28%, p=0.001).

In women who requested combined screening and presented to our office for nuchal translucency ultrasound, 69 (2.8%) were found to have a non-viable pregnancy, 16 (0.6%) women declined further screening following 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 1). In all, 58% were aged 35 years or older (Table I). With regard to ethnic background, 69% were Caucasian, 18% were Asian, 4.8% were Hispanic, 1.6% were African American, and the remaining 1.1% were of other ethnicities (Table II). The majority (87%) had private insurance .

In the 2310 women who received first trimester combined results, 1400 (60.6%) received instant results while 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 which required repeat collection, or requiring assistance with obtaining the sample. Only age >35 predicted greater likelihood of receiving instant results (p=0.001), while ethnicity and referring provider did not (Table I).

In an analysis of patients who did not receive instant results, 357 (15.4%) had biochemical screening performed prior to 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 prior to their NT appointment, 1400, or 80%, received an instant result.

We also compared the overall volume of patients seen in the clinic over the two 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% ($p=0.02$) and amniocentesis decreased by 6% ($p=0.049$) (Table III). In the time frame evaluated in this study, 10.2% of CVS procedures were done following first trimester combined screening. 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 due to increased risk identified by first trimester combined screening.

Comment

First trimester combined screening 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 first trimester combined screening 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 greater. 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 prior to making that decision.

Of the women who collected their biochemistry sample prior to 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.

It is often discussed that women vary in their approach to prenatal diagnosis and screening based on 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 choice⁶, acculturation and language skills^{7,8}, risk perception, attitudes toward abortion and health care systems in general, and values such as fatalism⁹. 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 first trimester combined screening 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, first trimester combined screening 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 definitive result. In evaluating the obstacles to obtaining blood such that instant results were available, nearly 15% of patients sent the blood sample prior to 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 due to 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 first trimester combined screening becomes more widespread. Consequently, more providers trained in CVS will be required.

While our study presents an assessment of one approach to the provision of first trimester combined screening, 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. Additionally, we lacked some information on the women with respect to income and education level that may predict both choice of and success in utilizing 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 first trimester combined screening 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.

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Figure 1.
Flow diagram illustrating results of first trimester screening program.

Table I

Percentage of women receiving instant results by maternal age.

MATERNAL AGE	INSTANT RESULT	LATER RESULT	TOTAL
≥35	846 (63.4%) [*]	488 (36.6%)	1334
<35	554 (56.8%)	422 (43.2%)	976
	1400 (60.6%)	910 (39.4%)	2310

*
p=0.001 for age ≥35 vs <35 years.

Table II

Percentage of women receiving instant results by ethnic background.

ETHNICITY	INSTANT RESULT	LATER RESULT	TOTAL
African-American	23 (51.1%)	22 (48.9%)	45
Caucasian	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
	1400	910	2310

Differences not significant between ethnic groups (p=0.2291).

Table IIIPatient Volume and Procedures 24 months prior versus 1st 24 months Combined Program

	11/1/01-10/31/03	11/1/03-10/31/05	
CVS *	759 (28%)	852 (31%)	p=0.003
Amniocentesis	1982 (72%)	1860 (69%)	
Total Procedures	2741	2712	
Total Patient Volume	7047	8343	

* CVS as proportion of total procedures.