OBSTETRICS

Uptake of noninvasive prenatal testing at a large academic referral center

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OBJECTIVE: Noninvasive prenatal testing (NIPT) is a recently developed risk-assessment technique with high sensitivity and specificity for fetal aneuploidy. The effect NIPT has had on traditional screening and diagnostic testing has not been clearly demonstrated. In this study, NIPT uptake and subsequent changes in the utilization of first-trimester screen (FTS), chorionic villus sampling (CVS), and amniocentesis in a single referral center is reported.

STUDY DESIGN: Monthly numbers of NIPT (in high-risk patients), FTS, CVS, and amniocentesis were compared between a 35-month baseline period (April 2009 through February 2012) before introduction of NIPT, and the initial 16 months following NIPT introduction divided in 4-month quarters beginning in March 2012 through June 2013.

RESULTS: A total of 1265 NIPT, 6637 FTS, 251 CVS, and 1134 amniocentesis were recorded over the 51-month study period in singleton pregnancies of women who desired prenatal screening and diagnostic testing. NIPT became the predominant FTS method by the second quarter following its introduction, increasing by 55.0% over the course of the study period. Total first-trimester risk assessments (NIPT+FTS) were not statistically different following NIPT ($P = .312$), but average monthly FTS procedures significantly decreased following NIPT introduction, decreasing by 48.7% over the course of the study period. Average monthly CVS and amniocentesis procedures significantly decreased following NIPT introduction, representing a 77.2% and 52.5% decrease in testing, respectively. Screening and testing per 100 morphological ultrasounds followed a similar trend.

CONCLUSION: NIPT was quickly adopted by our high-risk patient population, and significantly decreased alternate prenatal screening and diagnostic testing in a short period of time.

Key words: first-trimester screen, noninvasive prenatal testing, prenatal diagnosis, prenatal screening

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Noninvasive prenatal testing (NIPT) uses cell-free fetal DNA fragments acquired from maternal blood to detect imbalances in fragments originating from chromosomes 21, 18, and 13, and the sex chromosomes, and has the potential to dramatically alter previous screening paradigms for fetal aneuploidy. Validation studies have shown this technology to be highly sensitive and specific, with low false-positive rates (<1%),[1-3] resulting in many national and international societies recommending its incorporation into current screening methodologies for high-risk patients.[4-6] Previously, prenatal risk assessment used a combination of serum markers, ultrasound findings, or both during the first and second trimester to establish a patient-specific risk for fetal aneuploidy. The limitation of these screening algorithms is the suboptimal sensitivity (85-95%) and screen-positive rate (5%) of first-trimester screening (FTS) and second-trimester screening requiring many invasive procedures such as chorionic villus sampling (CVS) or amniocentesis to be performed for every true-positive diagnosis.

The First- and Second-Trimester Evaluation of Risk Trial in the United States and the Serum, Urine, and Ultrasound Screening Study in the United Kingdom confirmed that to achieve an 85% detection rate for Down syndrome during the 12th week of pregnancy required a 5% screen-positive rate.[7,8] In addition, to achieve the highest sensitivity (90-95%) fully integrated or stepwise sequential risk assessment required a second visit with need for coordinated patient follow-up and compliance. Screen-positive women then required an invasive diagnostic procedure that posed a risk that has been reported to be as high as 1% for maternal or fetal complications.[9] This led to many unnecessary diagnostic procedures and subsequent pregnancy loss.

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NIPT has the potential for circumventing these clinical challenges by offering higher sensitivity (>99%) and specificity with a lower false-positive rate (<1%). Large-scale validation trials have shown that NIPT can identify a number of fetal aneuploidies, including a >99.1% detection rate for Down syndrome.[1-3] Positive attributes reported of NIPT from women who underwent testing were the ease of use, decreased risk to the fetus, and opportunity for earlier decision-making regarding the course of their pregnancy.[10] NIPT can be merged with current testing practices to function either as a first-line screen in high-risk women, or as an advanced screen prior to diagnostic testing for women who are screen-positive using conventional methods.[11] Formal recognition of the utility of NIPT in high-risk women by the American Congress of Obstetricians and Gynecologists (ACOG) and the Society of Maternal-Fetal Medicine occurred in December 2012, with many centers only recently implementing NIPT in their clinical practice.[4] Our center offered NIPT to high-risk women beginning in March 2012, 9 months prior to ACOG Committee Opinion concerning NIPT use, and as early adopters, our institution now has considerable experience with the implementation of NIPT in clinical practice.

The impact that NIPT has had on prenatal screening methods, such as combined FTS and invasive testing with CVS and amniocentesis, has not been reported in a single large practice in the United States. In this study, the effect that introduction of NIPT has had on other prenatal screening and diagnostic procedures in a single referral center is reported.

Materials and Methods

The study design involved a retrospective analysis of an independently adjudicated and prospectively collected database comprising all consecutive patients who received FTS, amniocentesis, or CVS beginning in April 2009 and NIPT after March 2012 and ending in June 2013. These data were collected through billing records and the genetic counseling program as part of a quality assurance protocol in the division of maternal-fetal medicine. The number of FTS, CVS, and amniocentesis were collected using *Current Procedural Terminology* (*CPT*) codes from billing records of the maternal-fetal medicine department, a large-volume, academic referral center consisting of 3 sites underneath the Eastern Virginia Medical School umbrella of services. Monthly CVS counts were determined using *CPT* code 59015, while monthly amniocentesis counts were determined using *CPT* code 59000. Amniocenteses for nongenetic indications were excluded from our analysis, as determined by a review of the patient's medical record. The number of FTS was determined using *CPT* code 76813, which is the billing code for first-trimester fetal nuchal translucency measurement in a singleton pregnancy. FTS for multiple pregnancies uses a different *CPT* identifier and was not included in our analysis. The number of screening and diagnostic tests was compared before and after NIPT introduction to determine NIPT uptake and its effect on other prenatal testing programs.

Monthly rates of all 4 tests were compared between a 35-month period (April 2009 through February 2012) representing the baseline institutional experience before NIPT introduction, and the initial 16-months following introduction of NIPT at our institution (March 2012 through June 2013). This 16-month time period was divided into 4 equal quarters consisting of 4 months in each quarter: first quarter, March through June 2012; second quarter, July through October 2012; third quarter, November 2012 through February 2013; and fourth quarter, March through June 2013.

The subject population included all referred patients who presented to our perinatal practice and opted to undergo prenatal testing. The patients represent a cross-section of varying socioeconomic statuses with insurance coverage typical of southeastern Virginia. The majority of patients were referred for genetic counseling by community obstetricians who did not provide this service. Patients were initially seen by specially trained certified genetic counselors who discussed the risks, benefits, and clinical implications of screening and diagnostic testing and obtained informed consent from the patient for their chosen option. Patients were subsequently counseled by 1 of 8 maternal-fetal medicine specialists, and the patient finalized her choice.

FTS was described as a screening method available beginning in the first trimester using ultrasound measurement of the nuchal translucency and serum analytes for both high- and low-risk patients with an 85% detection rate for Down syndrome and a 5% false-positive rate.[7] NIPT was introduced in March 2012 to patients with a singleton pregnancy and considered at high risk for fetal aneuploidy due to advanced maternal age, a history of fetal aneuploidy, or positive result of a previously performed screen. Women who screened positive on an earlier screen were offered NIPT in addition to going directly to a diagnostic test such as CVS and amniocentesis. NIPT was described as a noninvasive screening test involving a blood draw with >99% sensitivity and <1% screen-positive rate.[1,2] The description of the test was unchanged over the course of the study period, including after society recommendations. NIPT was only offered to singleton pregnancies. Other screening and testing modalities were also offered to patients in addition to FTS and NIPT. Patients were also instructed that some insurance companies would not fully reimburse NIPT and patients were encouraged to discuss any further questions with their individual insurance programs. NIPT assays were performed by 1 of 4 commercial laboratories.

CVS and amniocentesis were described as invasive procedures that incurred an intrinsic risk of pregnancy loss in 1 of every 100-300 procedures, but offered a >99.9% sensitivity rate for Down syndrome and other chromosomal aneuploidies. Patients were instructed that only diagnostic testing through either CVS or amniocentesis could definitively identify fetal