Utilization of noninvasive prenatal testing: impact on referrals for diagnostic testing

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OBJECTIVE: Since the introduction of noninvasive prenatal testing (NIPT), a marked decrease in prenatal diagnostic testing (chorionic villus sampling [CVS] and amniocentesis) has been observed with unknown potential effects on genetic diagnosis of these pregnancies. The purpose of this study was to understand the impact of NIPT on genetics counseling referrals, diagnostic testing with CVS/amniocentesis, and appropriate use of NIPT.

STUDY DESIGN: A retrospective cohort study was performed on all women referred for genetic counseling and prenatal testing during the 2 years preceding the introduction of NIPT (pre-NIPT) and 2 years following (post-NIPT). The primary outcome was the difference in the number of women referred for genetic counseling and prenatal diagnosis during the pre-NIPT period compared with the post-NIPT period. The secondary outcome was the difference in the number of women referred who were not considered candidates for NIPT between the 2 study periods.

RESULTS: There was a statistically significant reduction in the number of referrals for genetic counseling and diagnostic testing in the post-NIPT compared with the pre-NIPT period (2824 vs 3944, $P = .001$), a reduction of 28.4%. During the post-NIPT period there was a significant reduction in referrals of women who would not be candidates for NIPT (467 pre-NIPT vs 285 post-NIPT, $P = .043$). In women who had diagnostic testing with CVS during the study period, 32.4% of the aneuploidies identified would not have been detected by NIPT.

CONCLUSION: There was a significant reduction in the number of patients referred for genetic counseling and prenatal diagnosis following the introduction of NIPT. In addition, there was a significant reduction in the number of patients referred for counseling and testing who would not be candidates for NIPT. This suggests that an increasing number of potential patients are being offered NIPT screening instead of diagnostic testing, including those at risk for fetal single gene disorders and aneuploidies not detectable by NIPT, potentially leading to misdiagnosis.

Key words: amniocentesis, chorionic villus sampling, noninvasive prenatal testing, prenatal diagnosis

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Over the past few years, several studies have evaluated the use of cell-free fetal DNA from maternal plasma for detection of fetal aneuploidy. These studies have demonstrated detection rates of ≥99% for trisomy 21 and trisomy 18, and a detection rate of 91% for trisomy 13.[1-3] In October 2011, noninvasive prenatal testing (NIPT) for detection of trisomy 21 was introduced into clinical practice. Subsequently, in the spring of 2012, detection of additional trisomies (chromosomes 13 and 18) was incorporated into clinical testing. Since the introduction of NIPT, a dramatic rise in the use of NIPT by women at increased risk for fetal aneuploidy has been reported,[4] with a potential decrease in the use of first-trimester screening and invasive genetic testing, including chorionic villus sampling (CVS) and amniocentesis.[5]

This rapid increase in utilization of NIPT may be influenced by the marketing efforts of the laboratories performing NIPT and increasing patient concerns that invasive diagnostic testing is associated with adverse pregnancy outcomes.[6] A survey of obstetricians, both academic and private practice based, predicted that they would offer NIPT to women at high (86.1%) and average (76.2%) risk within 12 months.[7] Even patients may be directly influenced, as only 20% of women reported that they would do whatever their doctor recommended regarding NIPT.[8] In a study of factors affecting the clinical use of NIPT, Skirton and Patch[9] found that "Ease of use, decreased risk to the fetus, and opportunity for earlier decision-making regarding the course of their pregnancy" were reported by women as reasons for choosing NIPT. In another study, the single most important factor for choosing NIPT was reported to be safety to the fetus (75%) whereas accuracy of results was identified as the most important factor by only 13% of women.[8] Recent studies show that, in pregnancies that had a positive screen for Down syndrome, there was a significant

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TABLE 1
Characteristics of women referred for prenatal diagnosis and screening

Characteristic/indication for referral (women may have >1 indication or test)	Pre-NIPT (n = 3944)	Post-NIPT (n = 2824)	*P* value
Advanced maternal age	3521 (89.3%)	2242 (79.4%)	.001
Positive first- or second-trimester screen	530 (13.4%)	350 (15.6%)	.26
Noncandidate for NIPT			
Single gene disorder	102 (2.6%)	50 (1.7%)	.028
Balanced translocation carrier	22 (0.6%)	12 (0.5%)	.45
Multiple gestation	312 (7.9%)	159 (8.6%)	.36
Vanishing twin	31 (0.8%)	18 (0.6%)	.48
Total noncandidate for NIPT	467 (11.8%)	285 (10.1%)	.043
Declined diagnostic procedure	1034 (26.2%)	875 (31.0%)	.001
Noninvasive screening			
First- and/or second-trimester screen	644 (16.3%)	853 (30.2%)	< .001
NIPT	0	583 (20.6%)	–
Diagnostic procedures			
CVS	2476 (63.1%)	1773 (62.8%)	.56
Amniocentesis	331 (8.4%)	201 (7.1%)	.47
All diagnostic procedures	2807 (71.2%)	1974 (69.9%)	.31

CVS, chorionic villus sampling; *NIPT*, noninvasive prenatal testing.

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decline in the number of women who chose subsequent invasive genetic testing following the introduction of NIPT, despite potential concerns about using NIPT as a diagnostic test.[4,10] Thus, in view of these concerns regarding the perceptions and misperceptions of NIPT as a potential diagnostic test, and patient fear of invasive genetic testing, we wanted to understand the impact of NIPT on genetic counseling referrals and diagnostic testing with CVS/amniocentesis during the 2-year periods preceding and following the introduction of NIPT into clinical practice.

Materials and Methods

A retrospective cohort study using a natural experiment pre-NIPT and post-NIPT was conducted to compare a group of women referred to the Cedars-Sinai Prenatal Diagnosis Center for genetic counseling and prenatal testing from Jan. 1, 2010, through Dec. 31, 2011 (pre-NIPT) with women referred from Jan. 1, 2012, through Dec. 31, 2013 (post-NIPT). The primary outcome for the study was the difference in the number of women referred to our center for genetic counseling and prenatal diagnosis during the pre-NIPT period compared with the number of women referred during the post-NIPT period. The secondary outcome studied was the difference in the number of women referred who were not considered to be candidates for NIPT between the 2 study periods. Data collected included: the number of women referred for counseling and testing, the indications for referral, the number of women who accepted or declined diagnostic testing, and the number of women who were not candidates for NIPT. For purposes of the study, subjects who were not considered to be candidates for NIPT included women who were at risk for a fetus with a single gene disorder, parents who were carriers of a balanced chromosomal rearrangement (translocation or inversion), women who were carrying a multiple gestation, and/or who were identified by ultrasound to have a vanishing twin. For patients who chose to have a diagnostic procedure such as CVS or amniocentesis, all of the procedures were done at the Cedars-Sinai Prenatal Diagnosis Center. Additionally, karyotype results for patients who had CVS done from Jan. 1, 2010, through Dec. 31, 2013, were tabulated and analyzed. Statistical comparisons for categorical data were done using χ^2 analysis (SAS 9.4;SAS Institute Inc, Cary, NC). The Cedars-Sinai Medical Center Institutional Review Board approved this study.

Results

During the pre-NIPT period, 3944 women were referred for counseling and testing. In the post-NIPT period, 2824 women were referred for counseling and testing. This represents a significant decrease in referrals of 28.4% ($P = .001$). A comparison between the study groups is shown in Table 1. There was a statistically significant decrease in the referrals for advanced maternal age (89.3% vs 79.4%, $P = .001$). No differences in referral rate were observed for follow-up of a positive first-trimester combined or second-trimester quad screen, or integrated screening test. With respect to all patients who were considered noncandidates for NIPT, there was a 35% decrease in the referral rate (11.8-10.1%), which was statistically significant ($P = .043$). When specific indications were evaluated, there was a significant decrease in the referral rate for those who were at risk for single gene disorders (2.6% vs 1.7%, $P = .028$). However, for couples in which either parent was a carrier of a balanced chromosomal rearrangement, women with multiple gestations, and women with vanishing twins, the differences were not statistically significant. In addition, there was a statistically significant increase in the number of women who declined a diagnostic procedure following the introduction of NIPT: 26.2% vs 31.0% ($P = .001$). With respect to women who chose to have a noninvasive screening test, the percentage of women who had first- and/or second-trimester screening was significantly greater in the post-NIPT group (16.3% vs 30.2%,