Original Research

The effect of funding non-invasive prenatal testing (NIPT) on invasive procedures performed to identify trisomy 21 pregnancies: A population-based cohort study

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Abstract

Background: Screening for Trisomy 21 in Nova Scotia has traditionally included serum integrated prenatal screening (SIPS, maternal serum screening), and integrated prenatal screening (maternal serum screening with nuchal translucency, IPS) for those patients considered to be at high risk. In 2016, non-invasive prenatal testing (NIPT) became available as a funded second tier screen for pregnancies at high risk for Trisomy 21 in Nova Scotia.

Objective: To compare pregnancy characteristics and number of diagnostic procedures performed for high risk of Trisomy 21 before and after introduction of funded NIPT in Nova Scotia.

Methods: This population-based retrospective cohort study evaluated pregnancies with diagnostic testing and/or NIPT which were identified through the IWK Health Clinical Genomics Laboratory Database. Maternal chart review was performed for each pregnancy to confirm eligibility and collect demographic data. Descriptive statistics comparing number of diagnostic procedures and pregnancy characteristics were performed among two epochs – pre-NIPT (2012-2015) and post-NIPT (2016-2019) using Fisher's exact test, and rates of Trisomy 21 confirmed by diagnostic testing between the two epochs were described.

Results: The population incidence of Trisomy 21 remained stable and maternal demographics were similar between the two epochs; after the introduction of funded NIPT, the number of diagnostic procedures decreased, and when diagnostic testing was performed, the procedures were 6-fold more likely to confirm Trisomy 21 (95% CI 2.6-12.9) following high risk screening.

Conclusion: The decrease in diagnostic procedures with an increase in the prenatal detection of Trisomy 21 demonstrated in this study illustrates the value of NIPT in a population with limited resources for first trimester screening.

Introduction

Trisomy 21 is the most common chromosomal anomaly in newborns, with an incidence of approximately 1 in 750 Canadian live births[1]. In Canada, provincial options for Trisomy 21 screening are influenced by geographic limitations and available resources[2-4]. The Department of Health and Wellness in the province of Nova Scotia funds serum integrated prenatal screening (SIPS, integrating first and second trimester maternal serum screening, without inhibin A) for all women, or integrated prenatal screening (IPS), which includes nuchal translucency assessment in addition to the SIPS, for those considered to be at higher risk based on maternal age and other risk factors. SIPS and IPS are standard provincial aneuploidy screening. Tertiary level ultrasound for assessment of nuchal translucency is offered to individuals estimated to be at high risk of Trisomy 21 based on first trimester maternal serum screening alone (risk for Trisomy 21 ≥ 1:50), or assessment of soft markers[5] is offered to individuals estimated to be at high risk for Trisomy 21 based on either SIPS or IPS (risk for Trisomy 21 ≥ 1:304).

Prior to 2016 in Nova Scotia, invasive diagnostic testing via amniocentesis or chorionic villus sampling (CVS) would be offered to individuals at high risk for Trisomy 21 based on this first tier of standard aneuploidy screening (associated with an additional pregnancy loss rate likely < 0.5%)[6]. Since 2016, non-invasive prenatal testing (NIPT) has been funded as a second tier screen (offered with a high risk first tier screening result) as a next information step[2] to facilitate personal,

Table 1. Characteristics and outcomes in women undergoing prenatal diagnostic testing or funded NIPT for Trisomy 21, by epoch, Nova Scotia, Canada.

Characteristic	2012-2015 n (%)	2016-2019 n (%)	p value
Number having diagnostic testing or funded NIPT	184 (100)	538 (100)	
Maternal age ≥ 35 years	80 (43.5)	259 (48.1)	0.31
Nulliparity	73 (39.7)	186 (34.6)	0.12
Gestational age at testing*, weeks			
≤13+6	6 (3.3)	102 (19.0)	< 0.01
14+0 – 15+6	14 (7.6)	29 (5.4)	0.25
16+0 – 19+6	66 (35.9)	122 (22.7)	< 0.01
≥20	98 (53.3)	285 (53.0)	1.00
Type of test* for high risk result for T21			
CVS	6 (3.3)	9 (1.7)	0.31
Amniocentesis	178 (96.7)	58 (10.8)	< 0.01
NIPT	0 (0.0)	471 (87.6)	-
Prenatally diagnosed pregnancies with T21	8/184 (4.3)	18/67 (26.9)	0.01

** Test = prenatal diagnostic testing or funded NIPT*
NIPT, non-invasive prenatal testing; T21, trisomy 21; CVS, chorionic villous sampling

informed choice6. NIPT technology uses cell-free DNA in maternal plasma to improve performance over traditional screening modalities for Trisomy 213,7. Due to the high negative predictive value of NIPT (>99%)[8], a low-risk result allows women the option to avoid diagnostic procedures and decreases maternal anxiety[9,10].

A retrospective population-based database study was undertaken to describe temporal changes in prenatal and postnatal diagnoses of Trisomy 21 before and after the introduction of funded NIPT as a second tier screen.

Methods

This population-based retrospective cohort study used data derived from the IWK Health Clinical Genomics Laboratory Database (CGLD), combined with maternal health records review, from January 1, 2012 to December 31, 2019. The CGLD database is population-based and contains secure cytogenetic and molecular genetic testing information (such as indication for testing, sample types, and test results) housed within the IWK Clinical Genomics Laboratory, and provides service for all provincially funded tests for the three Maritime Provinces, including Nova Scotia. The CGLD was used to identify all pregnancies for which diagnostic testing and/or NIPT were performed for a high risk standard aneuploidy screening result for Trisomy 21. Pregnancies with prenatal diagnoses of structural anomalies were excluded since NIPT is not offered as a funded test for these patients. Pregnancies for which diagnostic testing was performed for any other indication (including Trisomy 13 or Trisomy 18) were also excluded. The total number of prenatal and postnatal diagnoses of Trisomy 21 was extracted from this database.

For each pregnancy in which either NIPT or a prenatal diagnostic test was done for the indication of high risk for Trisomy 21, maternal health records reviews were performed to obtain data on maternal age, parity, pregnancy plurality, history of previous pregnancy affected by Trisomy 21, gestational age at the time of testing, and testing results.

A descriptive analysis of the study population was undertaken, reporting the number of tests and cases of Trisomy 21. Rates were grouped in two epochs, 2012-2015 and 2016-2019, which represented timeframes before and after the introduction of funded NIPT as a second tier screening method in Nova Scotia. Comparisons of demographic characteristics between epochs were made using Fisher's exact test, and rates of Trisomy 21 confirmed by diagnostic testing between the two epochs were described. Analyses were performed by IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA). Aggregate cell sizes of 1-4 were suppressed to protect patient privacy, in compliance with local data management principles.

Results

As shown in Table 1, among pregnancies without identified structural anomalies predicted to be at high risk for Trisomy 21 with standard aneuploidy screening modalities, 184 individuals undertook invasive diagnostic testing in 2012-2015 (pre-NIPT epoch), whereas 538 individuals undertook second tier screening with either NIPT and/or invasive diagnostic testing in 2016-2019 (post-NIPT epoch). Maternal age, parity, and history of previous Trisomy 21 did not differ among those tested between the two epochs (p>.05). The proportion of twin pregnancies was higher in 2016-2019 compared to

2012-2015 (p=.03). In addition, the proportion of NIPT and/or invasive diagnostic testing done in the first trimester (≤13+6 weeks) was higher (19.0%) in 2016-2019 compared to 3.3% in 2012-2015 (p < .001). Additionally, the proportion of diagnostic tests performed in the first trimester was higher (11.1%) in 2016-2019 compared to 3.3% in 2012-2015 (p = .03).

The number of invasive tests performed decreased from 184 in 2012-2015 to 67 in 2016-2019. Of these women, 4.3% (8/184) in 2012-2015 and 26.9% (18/67) in 2016-2019 were positive for Trisomy 21, meaning that the positive predictive value for the screening algorithm after 2015 was 6.2 times higher (95% CI: 2.9, 13.7).

Prior to funded NIPT, 27 total cases of Trisomy 21 were identified, of which eight (29.6%) confirmed diagnoses were made prenatally and 19 (70.4%) were made postnatally or among cases of intrauterine fetal demise. Cases detected postnatally in 2012-2015 included those because of declined or failed screening, or because patients chose expectant management after a high risk standard screening result. After the initiation of funded NIPT, in which 28 cases of Trisomy 21 were identified, 18 (64.3%) were detected prenatally, and ten (35.7%) postnatally because standard screening by IPS/SIPS was declined or failed. Thus, the proportion of cases detected prenatally was 2.2 times higher (95% CI: 1.1, 4.1) in 2016-2019 compared to 2012-2015.

For reference, the total Trisomy 21 diagnoses in the population (including prenatal, postnatal and intrauterine fetal demise cases in both fetuses affected and unaffected by anomalies) from 2012-2015 was 88, while from 2016-2019 the total was 73; the total number births and pregnancy losses is not available in the CGLD for these timeframes, and therefore the incidence of Trisomy 21 in the population could not be calculated.

Discussion

This population-based cohort study in Nova Scotia described the pattern of diagnosis of Trisomy 21 four years before and four years after the introduction of publicly funded NIPT as a second tier screen for pregnancies determined to be at high risk for Trisomy 21 following local standard aneuploidy screening. The proportion of cases that were detected prenatally more than doubled, while the number of diagnostic procedures performed decreased by 64%. After implementation of funded NIPT, differences were noted in gestational age at testing, with an increase in testing at less than 14 weeks.

Prior to the introduction of funded NIPT in Nova Scotia, options for women screening positive for Trisomy 21 using standard aneuploidy screening included expectant management, self-funded NIPT, or diagnostic testing. For high risk women identified in the first trimester, the high sensitivity of NIPT for Trisomy 21 (99.3%) compared to traditional screening (83% for IPS) allows earlier diagnostic testing; the specificity of NIPT (99.8%) compared to traditional screening (97.9% for IPS) provides earlier reassurance compared to traditional screening[2,3]. The current study demonstrated that NIPT improved access to care, evidenced by both an overall reduction in diagnostic tests for pregnancies not affected by Trisomy 21 and a relative shift in gestational age for second tier investigation via diagnostic testing or funded NIPT, or diagnostic testing alone, from early second trimester (16+0 to 19+6 weeks) to the first trimester for pregnancies affected with Trisomy 21. Improving access to early diagnosis of fetal Trisomy 21 facilitates personal, informed choice, including continuation of pregnancy[6]. Similar results have been observed in two previous studies using data from Quebec, Calgary, Vancouver and Ontario[11,12]. In addition, rates of prenatal diagnosis were improved following the introduction of funded NIPT, suggesting that women who previously may have declined prenatal diagnostic testing would undertake funded NIPT as a second tier screen since it does not pose additional risk of pregnancy loss. Pregnancies complicated by fetal Trisomy 21 in this population and others have been shown to be at increased risk for adverse perinatal outcomes, including fetal demise[13]. Therefore, knowing (positive diagnostic test) or suspecting (high risk NIPT) fetal Trisomy 21 prompts the initiation of increased fetal surveillance and early delivery planning.

This study was able to examine provincial data from pregnancies at high risk for Trisomy 21 based on screening information before and after the introduction of funded NIPT, in order to evaluate selection of NIPT and diagnostic testing options for the indication of high risk for Trisomy 21. The current study was not able to identify women who were offered and declined diagnostic testing from 2012 to 2015, or women who were offered and declined funded NIPT or diagnostic testing from 2016 to 2019, since the number of all high risk screen results was not available in the CGLD. Selecting a population of all women with high risk standard screening for Trisomy 21, instead of a population of women with second tier screening results, may have provided additional information on personal, informed choice, but would have been impracticable since the screening and testing provincial database systems are separated at the present time. Cost-effectiveness studies suggest that contingent NIPT may be more cost effective than undergoing diagnostic testing[14-16], although this evaluation was beyond the scope of our study.

The results of this population-based cohort study

provide an example of how NIPT may be used to improve care in a population with limited resources for first trimester aneuploidy screening, since nuchal translucency risk adjustment (SIPS) is only available in Nova Scotia for populations identified as high risk for maternal or fetal disorders. NIPT provides information earlier in pregnancy and reduces the number of invasive diagnostic tests that are associated with an increased risk of pregnancy loss.

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