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Second-tier non-invasive prenatal screening for Down syndrome in a public obstetric unit: the first 12 months

Horace HC CHEUNG, MB ChB, LMCHK, M Med Sci
Lai-Yin TONG, RNM
William WK TO, MBBS, MPH, M Phil, MD, FHKAM(O&G), Cert HKCOG (MFM)
Department of Obstetrics and Gynaecology, United Christian Hospital

Objective: To review the uptake rate of non-invasive prenatal testing (NIPT) in the first 12 months of implementation in the obstetric unit of United Christian Hospital.
Methods: Between December 2019 and November 2020, women with a fetal Down syndrome (DS) risk ratio of ≥1:250 after first-trimester DS screening (using maternal serum markers and nuchal translucency thickness on ultrasonography) or second-trimester DS screening (using maternal serum markers) were offered free-of-charge second-tier NIPT or invasive testing. Results of NIPT and invasive testing and pregnancy outcome of these women were reviewed. Characteristics of those opting for NIPT versus invasive testing were compared. Univariate and logistic regression analyses were used to determine significant factors associated with opting for NIPT.
Results: During the study period, 2182 women underwent first-trimester DS screening (n=2086) or second-trimester DS screening (n=96). 117 women were screen positive, with a DS risk ratio of <1:250. The screen-positive rate was 5.36% overall and 5.23% for first trimester and 8.33% for second trimester. Of the 117 women, 26 had NIPT in private settings before or after being screened positive, 89 opted for NIPT (n=65) or invasive testing (n=24) in our hospital, and two did not have further testing owing to spontaneous miscarriage (n=1) or termination of pregnancy (n=1). Of 91 women with NIPT, 84 (92.3%) were at low risk for common aneuploidies, four were at high risk for T21 (n=2) or T18 (n=2), and three had abnormalities other than common aneuploidies. Six of the high-risk women underwent invasive testing and abnormalities were confirmed. Of the 24 women who opted for invasive testing, 14 had normal results and 10 had abnormal results. In logistic regression analysis, predictors for opting for invasive testing (rather than NIPT) were presence of abnormalities on ultrasonography (odds ratio (OR)=13.9, p=0.01), a nuchal translucency thickness of ≥3 mm (OR=7.62, p=0.01), and education level below tertiary level (OR=7.14, p=0.02).
Conclusion: In the first 12 months of implementation in United Christian Hospital, the uptake rate of NIPT as a second-tier test after positive DS screening was 77.8%, which is higher than that reported in previous studies when NIPT was a self-financed test.

Keywords: Down syndrome; Noninvasive prenatal testing

Introduction

Down syndrome (DS), or trisomy 21 (T21), is one of the few autosomal trisomies that allow continued fetal development and livebirth with prolonged survival, despite causing significant physical and neurodevelopmental delays and disabilities. In Hong Kong, prenatal screening and diagnosis of DS has evolved from direct invasive testing for all women with advanced maternal age to second-trimester DS screening (using maternal serum markers) and then to first-trimester DS screening (using both maternal serum markers and nuchal translucency thickness on ultrasonography). Since 2010, universal DS screening has been offered in all public obstetric units in Hong Kong[1].

Non-invasive prenatal testing (NIPT) for DS has a detection rate of 99.2% and a false-positive rate of 0.09%, which are better than the respective rates of 90% and 3.4% to 5.4% by first-trimester DS screening (using both maternal serum markers and nuchal translucency thickness on ultrasonography)[2-5]. NIPT reduces the need for invasive prenatal diagnostic tests, including chorionic villus sampling and amniocentesis, which carry a procedure risk of miscarriage of 0.1% to 0.2%6. However, NIPT is not a diagnostic test, as it occasionally gives non-reportable or false positive results[7]. A positive result requires confirmation by direct invasive testing[8,9]. Chromosomal aberrations other than the common aneuploidies may not be detected by NIPT that does not target these abnormalities[8,10].

In 2011, NIPT was first available in Hong Kong as a self-financed examination[11]. In the last quarter of

Correspondence to: Dr Horace CHEUNG
Email: chc997@ha.org.hk

2019, NIPT was implemented in all public obstetric units as a formal second-tier test for women with positive conventional DS screening, with an objective to reduce the need for invasive testing rather than to boaster the detection rate for DS. We review the uptake rate of NIPT in the first 12 months of implementation in the obstetric unit of United Christian Hospital.

Methods

This study was conducted at an obstetrics unit of United Christian Hospital, which manages 3500 deliveries per year. Between December 2019 and November 2020, women with <14 weeks gestation at booking were offered first-trimester DS screening, which includes ultrasonographic measurements of crown-rump length and nuchal translucency thickness, as well as assays of maternal serum markers of pregnancy-associated plasma protein A and free beta human chorionic gonadotrophin. Women with gestation between 14 and 19 weeks 6 days were offered second-trimester DS screening, which includes assays of maternal serum markers of serum alpha fetal protein, oestriol, inhibin A, and free beta human chorionic gonadotrophin. Those with a fetal DS risk ratio of ≥1:250 were considered screen positive and were offered second-tier NIPT, which is based on massive parallel sequencing techniques to detect common aneuploidies. Fetal sex is not routinely reported, but significant sex chromosomal aberrations, chromosomal duplications or deletions are reported selectively according to the discretion of the laboratory.

Within 1 week of results available, screen-positive women were invited by a designated midwife to attend a consultation regarding the risk ratio for DS, screen positivity for other aneuploidies such as trisomy 18 (T18) and trisomy 13 (T13), nuchal translucency thickness, and implications of having a baby with DS. The option of either NIPT or invasive testing (chorionic villus sampling or amniocentesis) was offered. The turn-around time for the former is <10 days and for the latter is <3 weeks. For invasive testing, quantitative fluorescent polymerase chain reaction (to exclude common aneuploidies) was used, followed by chromosomal microarray and/or karyotyping. The procedure-related miscarriage risk for chorionic villus sampling was 1% and for amniocentesis was 0.1% to 0.5%[6,11,12]. All screen-positive women were offered a detailed morphology scan at 20 weeks to exclude fetal structural abnormalities unless the NIPT or invasive testing already confirmed specific pathology.

Demographic data of all screen-positive women were retrieved from the Hospital Authority electronic database platforms, including the Antenatal Record System, the Specialty Clinical Information System, and the Clinical Management System, as well as from hardcopy records. In univariate analysis, characteristics of those opting for NIPT versus invasive testing were compared using the Chi-square test. Significant factors identified in univariate analysis were evaluated using the logistic regression analysis, with either NIPT or invasive testing as the dependent variable. A two tailed p value of <0.05 was considered statistically significant. SPSS (Windows Version 26, IBM Corp, Armonk, US) was used for statistical analysis.

Results

There were 2378 new antenatal bookings during the study period. Of 2268 eligible for DS screening, 86 opted out and were excluded and the remaining 2182 underwent first-trimester DS screening (n=2086, 92%) or second-trimester DS screening (n=96, 8%).

117 women were screen positive, with a DS risk ratio of <1:250. The screen-positive rate was 5.36% overall and 5.23% for first trimester and 8.33% for second trimester. Of the 117 women, 26 reported to have already had NIPT in private settings, 89 opted for NIPT (n=65) or invasive testing (n=24) in our hospital, and two opted out for further testing owing to spontaneous miscarriage (n=1) or termination of pregnancy after screen results showing nuchal translucency thickness of 5.1 mm and a DS risk ratio of 1:2 (n=1). Of 91 women with NIPT, 84 (92.3%) were at low risk for common aneuploidies, four were at high risk for T21 (n=2) or T18 (n=2), and three had abnormalities other than common aneuploidies (Figure). Among the seven women at high risk of abnormality, one woman at high risk for T18 underwent termination of pregnancy in a private hospital at 16 weeks after ultrasonography showed that the fetus had an omphalocoele and likely major congenital heart defects, and the remaining six women underwent invasive testing and were confirmed to have T21 (n=2), T18 (n=1), and other chromosomal aberrations (n=3). All six women underwent termination of pregnancy. One patient had a DS risk ratio of 1:15 but had a normal NIPT result in a private hospital. She insisted on undergoing amniocentesis at 16 weeks that showed a normal karyotype. Pregnancy outcomes of the 117 women are shown in Table 1.

Of the 24 women who opted for invasive testing, 14 underwent chorionic villus sampling and 10 underwent amniocentesis. Results were normal in 14 (58.3%) women. The remaining 10 women had T21 (n=2), T18 (n=4), T13 (n=1), other chromosomal aberrations (n=1), severe fetal

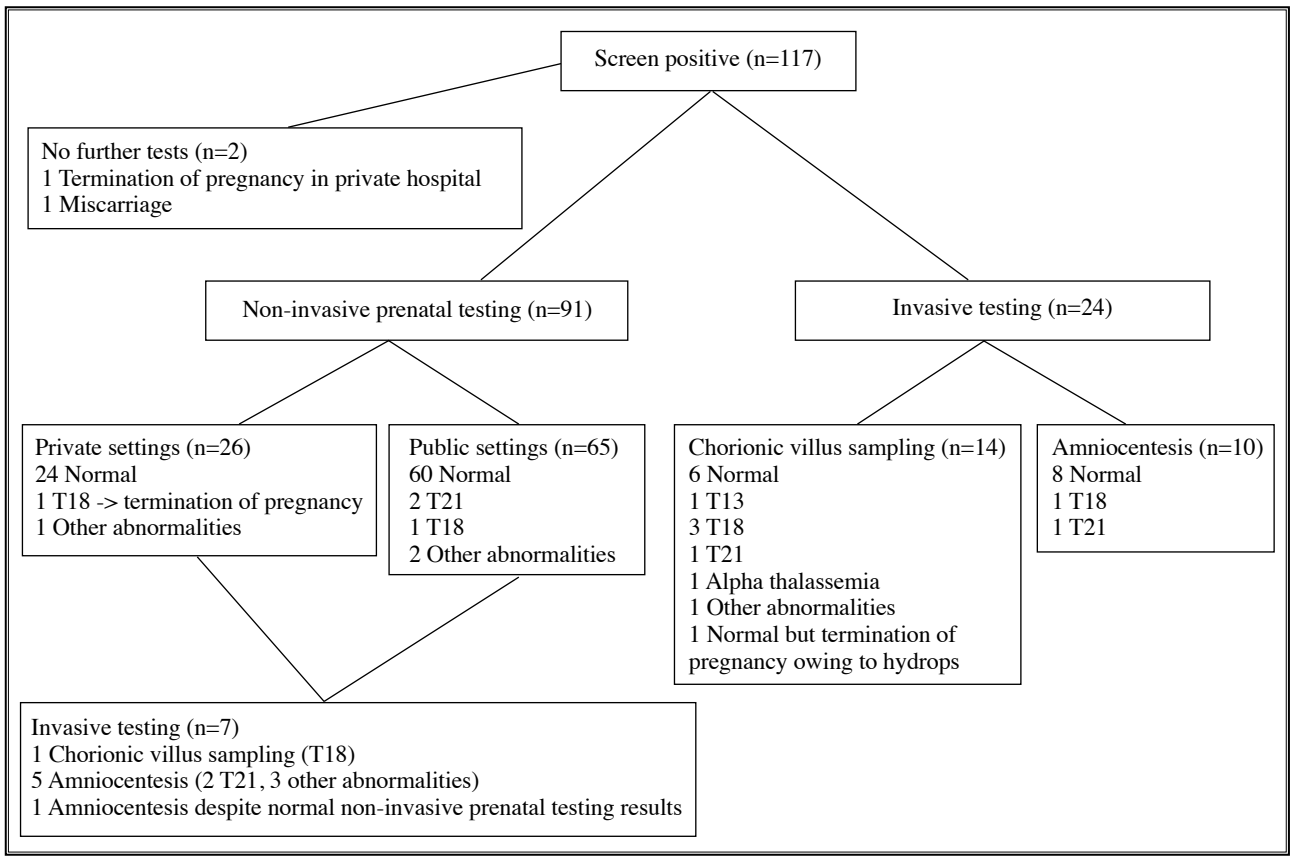

Figure. Flowchart of outcomes for 117 women with positive Down syndrome screening

Table 1. Pregnancy outcomes of 117 women

Pregnancy outcome	No. of women	Remarks
Term livebirths	96	-
Preterm livebirth	1	-
Spontaneous miscarriages	2	One had spontaneous miscarriage before any further testing One had normal non-invasive prenatal testing (NIPT) results
Termination of pregnancy	18	-
Chromosomal aberrations not detected	1	Ultrasonography showed fetal hydrops
No chromosomal microarray / karyotyping performed	2	One had Down syndrome risk and 1:2 cystic hygroma One had non-invasive prenatal testing (NIPT) showing high risk for T18
Chromosomal aberrations detected		
Trisomy 21	4	-
Trisomy 18	5	-
Trisomy 13	1	-
Alpha thalassemia major	1	-
Other chromosomal aberrations	4	46XY with 1.72 Mb copy loss in 2q13 (NIPT in private settings showed no abnormalities) 46,XX,der(18)ins(18;6)(q12;q15q22) [NIPT in private settings suspected 6q15-6q22.31 dup (31.39 Mbp); CMA of amniotic fluid sample showed 6q15q22.31x3] 46XX with 19.38Mb copy loss in 5p15.33-p14.3 (NIPT in public settings suspected copy number loss in chr5q15.3) 46 XY with interstitial deletion of 21.97 Mb in 21q11.2q22 (direct invasive testing with no NIPT performed)

Table 2. Characteristics of screen-positive women who opted for non-invasive prenatal testing or invasive testing

Characteristics	No further testing (n=2)	Non-invasive prenatal testing (n=91)	Invasive testing (n=24)	p Value
Ethnicity				0.87
Chinese	2	86 (94.5)	23 (95.8)	
Filipino	-	4 (4.4)	1 (4.2)	
Others	-	1 (0.1)	-	
Advanced maternal age ≥35 years	1	29 (31.9)	13 (54.2)	0.04
Education				0.001
Primary	-	-	5 (20.8)	
Secondary	-	42 (46.1)	12 (50)	
Tertiary	2	49 (53.9)	7 (29)	
Monthly family income, HK$				0.18
<20 000	-	16 (17.5)	5 (20.8)	
20 000-40 000	2	24 (26.3)	11 (45.8)	
40 000-60 000	-	34 (37.3)	5 (20.8)	
≥60 000	-	17 (18.6)	3 (12.5)	
Family history of abnormal babies or genetic disorders	-	-	-	-
Conception by assisted reproductive procedures	-	1 (1)	-	0.91
Parity				0.53
Nulliparous	1	29 (31.8)	8 (33.3)	
Multiparous	1	62 (68.2)	16 (66.7)	
Down syndrome screening				0.47
First trimester	2	84 (92.3)	23 (95.8)	
Second trimester	-	7 (7.7)	1 (4.2)	
Screen results				0.001
Positive for T21	2	85 (93.4)	16 (66.6)	
Positive for T18	-	2 (2.2)	4 (16.7)	
Positive for T21 and T18	-	4 (4.4)	4 (16.7)	
Down syndrome risk ratio		n=89	n=20	0.044
1:1-9	1	7 (7.9)	3 (15)	
1:10-100	-	28 (31.5)	11 (55)	
1:101-250	1	54 (60.6)	6 (30)	
Nuchal translucency thickness, mm		n=84	n=23	0.001
<3	1	73 (86.9)	11 (47.8)	
3-3.4	-	4 (4.8)	2 (8.7)	
≥3.5	1	7 (8.3)	10 (43.5)	
Presence of abnormalities on ultrasonography	1	7 (7.69)	6 (25)	0.028

* Data are presented as No. (%) of participants

hydrops (n=1) [together with a T21 risk ratio of 1:65 and a T18 risk ratio of 1:15 despite no chromosomal aberrations], or alpha thalassemia (n=1) [together with a nuchal translucency thickness of 3.9 mm, a DS risk ratio of 1:3, and known history of alpha thalassemia from previous pregnancies]. All 10 women underwent termination of pregnancy. One woman with a DS risk ratio of 1:65 but a normal NIPT had spontaneous miscarriage at 16 weeks.

In univariate analysis, compared with those who opted for NIPT, those who opted for invasive testing were more likely to have advanced maternal age (>35 years) [54.2% vs 31.9%, p=0.04], less likely to have tertiary education (29% vs 53.9%, p=0.001), more likely to be screen positive for T18 or both T21 and T18 (33.4% vs 6.6%, p=0.001), more likely to have a DS risk ratio of ≤1:100 (70% vs 39.4%, p=0.044), more likely to have a nuchal translucency thickness ≥3 mm (52.2% vs 13.1%, p=0.001), and more likely to have structural abnormalities detected on ultrasonography such as cystic hygroma, fetal hydrops, omphalocoele, congenital heart defects, single umbilical artery, suspected polydactyly, and fetal renal pelvic dilatation (25% vs 7.7%, p=0.028) [Table 2].

In logistic regression analysis, predictors for opting for invasive testing (rather than NIPT) were presence of abnormalities on ultrasonography (odds ratio (OR)=13.9, p=0.01), a nuchal translucency thickness of ≥3 mm (OR=7.62, p=0.01), and education level below tertiary level (OR=7.14, p=0.02) [Table 3].

Discussion

In the first 12 months of implementation of the free-of-charge second-tier NIPT in our obstetric unit, 77.8% of women with a positive conventional DS screening result opted for NIPT rather than invasive testing. The detection rate of DS and common aneuploidies by NIPT was 100%, with no false positives. There were no non-reportable cases from the Hospital Authority NIPT programme.

In a Hong Kong study in 2011-2012, the uptake rate of NIPT increased from 12.6% to 26.7% in the first 2 years as a self-financed test in public hospitals, whereas that of invasive testing decreased by 16.3% in the first year and by 25.6% in the second year[12]. In a study conducted from 2012-2013, the availability of NIPT after screen-positive for DS resulted in a 45% decrease in refusal to further testing and a decrease of invasive testing from 92.2% to 66.7%. Nevertheless, the overall uptake rate for NIPT was only 28.9% (362/1251)[13,14]. In 2014, when NIPT remained a self-financed item, 57.8% of women opted for NIPT as a second-tier test after screen positive, compared with 30.4% opting for NIPT as a primary screening test[14]. In 2015-2016, the uptake of NIPT in women with positive DS screening increased to 67%, whereas 31% opted for invasive testing and 2% had no further testing[11]. In 2015-2016, when NIPT was offered free-of-charge under a university research protocol, among 347 women with positive DS screening, 62.2% opted for NIPT and 37% opted for invasive testing with chromosomal microarray[15]. The NIPT uptake rate was not higher than that reported in previous studies despite similar costs and reporting time between options. In a study in the same period under similar settings, the NIPT uptake rate was 79% (207/262), with 31 women defaulted[16]. Financial arrangement affects the NIPT uptake rate in various settings in different counties[17-19]. In the present study, the NIPT uptake rate was 77.8%, but 28.6% of the NIPT were performed in private settings as a self-financed test although NIPT was offered free-of-charge in public hospitals. In 16 women, NIPT was performed in private settings as primary screening in parallel to the DS screening in our hospital. This highlights the preference of NIPT as the primary screening tool in some women. One study reported that 19.9% of women with positive DS screening already had a self-financed NIPT before taking DS screening test in public hospitals[15]. In the present study, 8.8% (8/91) of women did not wait for the consultation appointment and underwent further testing in private settings. Such behaviour underlines the high anxiety in decision making when informed of positive DS screening results[16,20]. In addition, private hospitals provide extended NIPT panels to identify sex chromosomes and atypical autosomal anomalies, in particular sex chromosome aberrations[8,21]. Currently, the NIPT in public settings do not report fetal sex, although major sex chromosomal aberrations are reported at the discretion of the laboratory. In a study of 260 women with NIPT, higher education level and higher NIPT knowledge score are associated with a preference for the extended NIPT report to the standard report[22]. In the present study, NIPT revealed one case of rare chromosomal aberration, which was confirmed by chromosomal microarray. The performance of the current NIPT in public settings is on par with international standards. Recent data have shown that the positive predictive values for detecting copy number variants, sex chromosomal aneuploidies, and selected microdeletions and duplications are around 60%, 40%, and 50%, respectively. These indicate a good scientific basis for expanded NIPT panels[23,24]. The option of revealing fetal sex could be added to enhance the current NIPT programme.

Although tertiary education and better NIPT knowledge are associated with NIPT uptake, only higher income is the independent predictor for NIPT uptake[25]. In addition, opting for NIPT are associated with nulliparity, first trimester status, advanced education, maternal employment, and conception by assisted reproductive techniques[11]. In North America during the early years of NIPT, NIPT was chosen by 43% of women who had a positive DS screening, 43% of women who had an ultrasonographic marker, and 36% of women who had an ultrasonographic abnormality[26]. NIPT is more likely to be chosen when

Table 3. Logistic regression analysis for predictors of opting for invasive testing over non-invasive prenatal testing

Variable	B	Standard error	Wald	P value	Odds ratio (95% confidence interval)
Presence of abnormalities on ultrasonography	2.63	1.07	6.07	0.01	13.9 (1.71-113.6)
Thick nuchal translucency ≥3 mm	2.03	0.784	6.70	0.01	7.62 (1.64-35.42)
Education level below tertiary level	-1.976	0.833	5.62	0.02	7.14 (1.41 -37.03)
Advanced maternal age ≥35 years	-0.156	0.608	0.07	0.79	1.17 (0.35 -3.84)
T18 risk positive (alone or combined with T21 positive)	0.004	0.001	0.17	0.68	1.01 (0.99-1.0)
T21 risk ratio >1:10	0.539	0.463	1.36	0.24	1.71 (0.69-4.24)

women perceive NIPT is widespread and routine, forward-thinking, and anxiety-relieving[27]. Our findings showed that NIPT was more likely to be chosen by women with more advanced education, which was consistent with previous local studies. Women with a higher knowledge score understand more about advantages and complicated issues of NIPT[14,22]. Nonetheless, the presence of ultrasonographic abnormalities or a thick nuchal translucency leads women to opt for invasive testing. This reflects the concerns of the women and the effects of counselling, as further invasive testing is indicated even if NIPT results are normal.

Fetal nuchal translucency of ≥3.5 mm is an indication for invasive testing by chromosomal microarray. However, in 522 fetuses with nuchal translucency thickness of 3.0 to 3.4 mm, up to 13.5% have a chromosomal aberration. Of them, 69% involve T21, T18, or T13, which are potentially detectable by NIPT. The residual risk for missing a (sub) microscopic chromosome aberration depends on the NIPT approach, ranging from 1:21 (for NIPT to detect only the common aneuploidies) to 1:464 (for genome-wide 10-Mb resolution NIPT). Thus, the nuchal translucency thickness cut-off for invasive testing should be 3.0 mm rather than 3.5 mm28. In public settings, diagnosis may be delayed because all abnormal NIPT results need to be confirmed by invasive testing. Thus, women should be allowed to opt for invasive testing earlier when nuchal translucency thickness is ≥3 mm.

There are some limitations to this study. The sample size is relatively small. Cumulative data from all public obstetric units should have included to better evaluate of the NIPT uptake in Hong Kong. Some women were not aware of the availability of free NIPT as a second-tier test at the time of booking and thus arranged NIPT in a private clinic. It is expected that the acceptance and uptake rates of NIPT will continue to rise. Further evaluation of NIPT uptake is warranted.

Conclusion

In the first 12 months of implementation in United Christian Hospital, the uptake rate of NIPT as a second-tier test after positive DS screening was 77.8%, which is higher than that reported in previous studies when NIPT was a self-financed test.

Contributors

All authors designed the study, acquired the data, analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As editor of the journal, WWK To was not involved in the peer review process of this article. All authors have disclosed no conflicts of interest.

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Data availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The patients were treated in accordance with the tenets of the Declaration of Helsinki. The patients provided written informed consent for all treatments and procedures.

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