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ORIGINAL ARTICLE

How do the trends in the prenatal diagnosis of aneuploidy change after a non-invasive prenatal test becomes available? A Japanese single center study

Junichi Hasegawa · Masamitsu Nakamura · Akihiko Sekizawa

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Abstract
Purpose To clarify the trends in the use of the prenatal diagnosis of and screening for aneuploidy after a non-invasive prenatal test (NIPT) was made available at a single Japanese hospital.
Methods The subjects included consecutive pregnant females who visited our hospital for maternal checkups and delivery between January 2012 and April 2014. After the subjects were divided into those who desired a prenatal diagnosis or screening before the availability of NIPT and those who did after the availability of NIPT, the frequencies of various prenatal diagnosis and screening procedures were compared between the two groups.
Results A total of 544 patients who visited the hospital before NIPT was available and 703 who visited the hospital after NIPT became available were analyzed. While only 16.2 % of pregnant females received a prenatal diagnosis or screening before the NIPT was available, 27.5 % of them considered undergoing a prenatal diagnosis or screening after the NIPT was available before genetic counseling, and 24.0 % ultimately received a prenatal diagnosis or screening following genetic counseling. Of these patients, 7.7 % underwent NIPT. First trimester ultrasound screening for chromosomal abnormalities was unlikely to be selected (from 12.9 to 10.5 %, $p = 0.212$), although the rate of amniocentesis significantly increased after genetic counseling (from 1.5 to 3.7 %, $p = 0.021$).
Conclusion Since NIPT became available in 2013, pregnant females have demonstrated a deep interest in obtaining a prenatal diagnosis and screening. Whereas some patients choose to forgo a screening after receiving genetic counseling, others prefer invasive diagnostic tests in contrast to screening.

Keywords Amniocentesis · Chorionic villous sampling · Chromosomal abnormality · Down syndrome · First trimester · Nuchal translucency · Ultrasound

J. Hasegawa (✉) · M. Nakamura · A. Sekizawa
Department of Obstetrics and Gynecology, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan
e-mail: hasejun@oak.dti.ne.jp

Introduction

The background of screening for chromosomal abnormalities in Japan is very different from that in Western countries. Indeed, prenatal genetic screening is performed in fewer than 5 % of all pregnancies in Japan [1], whereas such screening has been conducted using ultrasound and maternal serum markers starting in the first trimester in many other countries for many years [2–4]. However, the number of doctors able to provide accurate estimates of the probability of chromosomal abnormalities using ultrasound markers during the first trimester is limited in Japan due to the need for training and because the time allotted to complete ultrasound scans is very short. On the other hand, the demand for tests to predict abnormalities in the fetus is likely to increase steadily.

First trimester screening for chromosomal abnormalities requires experience with ultrasound as well as genetic counseling, and also requires a thorough understanding of the associated ethical concerns. In addition to the lack of reference values for ultrasound and serum marker parameters in Japanese patients, there has been a prohibition on mass screening for chromosomal abnormalities after maternal serum screening was introduced in the clinical guidelines in the 1990s by the Ministry of Health, Labour

and Welfare of Japan [1]. This is one reason why the use of first trimester screening in Japan lags behind that seen in Western countries. However, doctors at our university hospital certified by the Fetal Medicine Foundation in London began performing ultrasonographic scans during the first trimester in 2011. For clients requesting screening for fetal chromosomal abnormalities, nuchal translucency (NT) measurements and risk assessments by well-trained sonographers are now available under the support of genetic counselors.

Furthermore, the non-invasive prenatal test (NIPT) has been available in Japan since April 2013, and it has a high detection rate. Consequently, the rate of pregnant Japanese females relying on the prenatal diagnosis and screening for fetal anomalies has increased. We speculate that traditional screening tests with lower detection rates may be displaced by NIPT.

Therefore, the aim of the present study was to clarify the trends in the use of prenatal diagnosis and screening for aneuploidy after the NIPT became available.

Patients and methods

The subjects included consecutive pregnant females who first visited our hospital before 9 weeks of gestation to make appointments for maternal checkups and delivery at our hospital between January 2012 and April 2014. Patients who requested only a prenatal diagnosis or screening, and who were referred to our hospital due to suspicious abnormal ultrasound findings, were excluded.

The subjects were divided into those who desired a prenatal diagnosis or screening before the availability of NIPT (between January 2012 and March 2013), and those who desired testing after the NIPT became available (between April 2013 and April 2014). The frequencies of various prenatal diagnosis and screening tests were then compared between the two groups.

We explained prenatal diagnosis and screening for fetal chromosomal abnormalities using a booklet as follows whenever a pregnant female visited our hospital: the invasive diagnostic tests include amniocentesis and chorionic villous sampling, with an approximately 1:100 risk of miscarriage after the procedure, whereas first trimester ultrasound, quadruple test, and NIPT are considered to be screening tests without a significant risk to the fetus. Risk calculation of first trimester ultrasound was based on the maternal age and measurements of the nuchal translucency and crown-lump length according to the methods provided by the Fetal Medicine Foundation [5]. The detection rates in first trimester ultrasound and the quadruple test are about 80 %, and have a false positive rate of about 5 % [6, 7]. NIPT is available only for patients 35 years of age or older at delivery, those whose fetal ultrasonographic findings or serum marker levels indicate an increased risk of aneuploidy, those with a history of a prior pregnancy with a trisomy, or in cases of parental balanced Robertsonian translocation with an increased risk of fetal trisomy 13 or trisomy 21. Although NIPT detects approximately 99 % of fetuses with Down syndrome, it is not a diagnostic test, and the rate of false positives is approximately 0.1 % [8], so an invasive diagnostic test is required in cases where the screening result is positive. First trimester serum screening tests and/or combined tests using ultrasound and maternal serum marker assessments are not available at our institution; as such, screening is not established in the Japanese population and is available at only few institutions.

The patient cost of each procedure was 21,000 yen (about $200) for first trimester ultrasound screening or quadruple tests, 210,000 yen (about $2,000) for NIPT, and 130,000 yen (about $1,275) for chorionic villous sampling or amniocentesis at our institution.

The data were entered into a statistical software package [Statistical Package for Social Science (SPSS), Windows version 20.0 J; Chicago, IL, USA]. Categorical variables were reported as frequencies and compared using Fisher's exact test. Statistical significance was defined as p value <0.05. The research study was approved by the Ethics Committees of our hospital. Informed consent was obtained in writing from all of the patients. The confidentiality of the patients involved was protected, and no personal data were needed for the present study.

Results

A total of 1,247 subjects (544 who visited before NIPT was available and 703 treated after the introduction of NIPT) were analyzed. The frequencies of various prenatal diagnosis and screening tests as the first choice examination before and after the availability of NIPT are presented in the Table 1 While only 16.2 % of pregnant females received a prenatal diagnosis or screening before NIPT became available, 27.5 % of them considered a prenatal diagnosis or screening after NIPT was introduced, but before genetic counseling was provided, and 24.0 % of patients finally received a prenatal diagnosis or screening after the NIPT was available following genetic counseling. Of the patients who received a prenatal diagnosis or screening after genetic counseling, 7.7 % underwent NIPT.

On the other hand, first trimester ultrasound screening was unlikely to be selected (from 12.9 to 10.5 %, $p = 0.212$), although the rate of amniocentesis significantly increased after genetic counseling (from 1.5 to 3.7 %, $p = 0.021$).

Table 1 Trend of prenatal diagnosis and screening for chromosomal abnormalities as a first choice before and after NIPT availability

	Before NIPT 2012–2013 ($n = 544$)	After NIPT 2013–2014 ($n = 703$)	p value
Screening			
First trimester ultrasound	12.9 % (70)	Before GC 13.9 % (98)	0.616
		After GC 10.5 % (74)	0.061
Quadruple test	0.6 % (3)	Before GC 1.6% (11)	0.109
		After GC 1.4 % (10)	0.166
NIPT	NA	Before GC 8.0 % (56)	NA
		After GC 7.7 % (54)	NA
Diagnostic test			
Chorionic villous sampling	0.6 % (3)	Before GC 0.7 % (5)	1.000
		After GC 0.7 % (5)	1.000
Amniocentesis	1.5 % (8)	Before GC 3.3 % (23)	0.045
		After GC 3.7 % (26)	0.021
Total	16.2 % (88)	Before GC 27.5 % (198)	<0.001
		After GC 24.0 % (169)	<0.001

() number of cases, *NIPT* non-invasive prenatal test, *NA* not applicable, *GC* genetic counseling

Discussion

Since NIPT became available in 2013, pregnant females have demonstrated a deep interest in obtaining a prenatal diagnosis or screening; in fact, 24.0 % of pregnant patients received a prenatal diagnosis or screening after NIPT became available, while only 16.2 % of pregnant females underwent the testing before the availability of NIPT. Most of this increase was due to the introduction of NIPT.

Whereas some patients chose to forgo a screening after receiving genetic counseling, others preferred to undergo invasive diagnostic tests in contrast to screening. In fact, amniocentesis was frequently the first choice of test (and the rate increased from 1.5 to 3.7 % of patients), with an increased number of pregnant patients receiving a prenatal diagnosis or screening. Since the subjects included only consecutive pregnant patients who visited our clinic to book maternal checkups and delivery at our hospital, and excluded those who requested only a prenatal diagnosis or screening, or who were referred to our hospital due to abnormal ultrasound findings; the subjects in the present study enrolled before and after NIPT became available had almost the same background. Therefore, we believe our results provide a true account of the actual trends in the general public. It is plausible that there was an increase in amniocentesis due to the introduction of NIPT, because screenings for fetal aneuploidies often might make pregnant females more aware of potential conditions, and a diagnostic test could ease their apprehensions.

Although NIPT is categorized as a non-diagnostic screening test, the demand for it is increasing because of its high detection rate and non-invasive characteristics. On the other hand, since ultrasound screening continues to be chosen by approximately 10 % of pregnant females, this type of screening may continue to be in demand, because NIPT is too expensive and only available to patients who fulfil the criteria. To improve the accuracy of screening for chromosomal abnormalities and to increase the satisfaction of patients who do not meet the requirements for NIPT in Japan, the use of first trimester combined tests using ultrasound and maternal serum marker assessments may be necessary until NIPT is available to all pregnant females and the cost of NIPT decreases.

In conclusion, we herein demonstrated some of the recent trends in the prenatal diagnosis of and screening for fetal aneuploidy before and after the introduction of NIPT at our institution. At present, requests for prenatal diagnosis may vary from person to person in this country, in contrast to that observed in Western countries. We believe that the development of a framework to provide genetic counseling corresponding to individual situations is required.

Conflict of interest There are no financial or other relationships that could lead to a conflict of interest.

Ethical standards All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 1975 Declaration of Helsinki, as revised in 2008 (5). Informed consent was obtained from all patients included in the study.

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