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Noninvasive prenatal testing: more caution in counseling is needed in high risk pregnancies with ultrasound abnormalities

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ABSTRACT

Objective: Non-invasive prenatal testing (NIPT) is increasingly being used in prenatal aneuploidy screening. The objective of this study was to assess the positive predictive value in our cohort of 68 cases with positive NIPT result. In addition, we wondered if the use of NIPT in cases with ultrasound abnormalities is appropriate, given the limited number of chromosomes investigated.
Design: We performed confirmative invasive testing using karyotyping, fluorescence *in situ* hybridization (FISH) and/or high-resolution chromosomal microarray analysis.
Results: In line with the published data, the positive NIPT result was confirmed in 64.7% of cases. Inconclusive and negative NIPT results followed by cytogenetically pathologic findings were encountered in three and in five cases, respectively. Four of the five fetuses with negative NIPT but pathologic cytogenetic findings were born with several malformations and diagnosed right after birth with severe genetic conditions. Of note, in all of those four cases, NIPT was offered despite the finding of major fetal ultrasound abnormalities and despite the fact that the family would not have opposed invasive testing or pregnancy termination.
Conclusion: More education of health care providers and caution in counseling and interpretation of test results are needed in order to meet the challenges that this new test, which enriches our diagnostic options in prenatal testing, poses.

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Introduction

In the last few years, intensive efforts have been made to study the feasibility of non-invasive prenatal testing (NIPT) as a new prenatal screening option. Nowadays, it is considered the most effective screening test for aneuploidy in high-risk pregnancies [1–3]. In a recent meta-analysis the detection rates (DR) for trisomies 21, 18 and 13 were 99%, 96.8% and 92.1%, at false-positive rates (FPR) of 0.08%, 0.15% and 0.20%, respectively [4,5]. For monosomy X, the DR was 88.6% at a FPR of 0.12%, and for sex chromosome aneuploidies other than monosomy X the DR was 93.8% at a FPR 0.12%. The low FPR stimulated the question if invasive confirmation of abnormal NIPT findings is at all necessary. This consideration, however, did not take into account the actual positive predictive value (PPV). Recent studies indeed showed that the PPV is only in the range of 92.2–93% for trisomy 21, 58–76.6% for trisomy 18, 32.8–45% for trisomy 13, 23–38% for monosomy X and 67% for other sex chromosome aneuploidies [6–8]. Next to the questions of predictive values for the main trisomies, we wondered if the use of NIPT in high-risk pregnancies would be appropriate considering the limited spectrum of chromosomes investigated. We therefore evaluated the PPV in invasive samples received for confirmation testing of abnormal NIPT results from a variety of providers and report on our experience of unfavorable outcomes in high-risk pregnancies, which had normal NIPT.

Methods

For this evaluation we included all the samples, which were sent to our center for confirmatory testing following NIPT from

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April 2013 until December 2015. This comprises the amniotic fluid ($n = 52$) and the chorionic villi ($n = 16$) samples of 68 pregnant women, who all had had NIPT indicative of aneuploidy, the abort material and the amniotic fluid of two cases with an inconclusive NIPT result, the amniotic fluid of one case with negative NIPT, but ultrasound abnormalities, and the blood of five affected newborns referred for clinical assessment and genetic testing, who all had only NIPT prenatally (four negative and one inconclusive NIPT results).

NIPT was performed either using the Prendia test investigating all chromosomes (Genesupport, Lausanne, Switzerland), Panorama test investigating chromosomes 13, 18, 21, XY, five common microdeletions (Di George-syndrome in 22q11.2, Prader Willi/Angelmann-syndrome in 15q11-q13, 1p36 microdeletion-syndrome, Cri-du-Chat-syndrome in 5p15.2-15.3) and triploidy (Natera, San Carlos, CA, USA), Prenatest investigating chromosomes 13, 18, 21, XY (Lifecodexx, Konstanz, Germany) or Harmony test investigating chromosomes 13, 18 and 21 (Ariosa, San Jose, CA, USA). The techniques we applied for confirmatory testing comprised standard karyotyping, fluorescence *in situ* hybridization (FISH) and/or high-resolution chromosomal microarray analysis (CMA) (CytoScanHD arrays; Affymetrix, Santa Clara, CA, USA), according to standard protocols. Of note, we do not have ultrasound information of all the samples we received for confirmation testing. We asked the ultrasound descriptions only when babies with severe malformations were born, and for the two more examples we describe in the "Results" section.

Informed consent for publication was obtained in all three cases, for which a detailed description is provided.

The term high risk pregnancy in the literature includes cases with: advanced maternal age (AMA), abnormal maternal serum screening (MSS), family history of aneuploidy and abnormal ultrasound findings indicating an increased risk for aneuploidy (including by definition also abnormal NT) [9–11].

Results

Positive predictive value of NIPT

We confirmed the positive NIPT results in 44/68 cases, resulting in an overall PPV of 64.7%. In detail, we confirmed 30/32 cases of trisomy 21 (94%), 4/5 cases of trisomy 13 (80%), 4/4 cases of trisomy 18 (100%), 3/3 triple X (100%), 0/1 cases of XXY and 1/12 (8%) cases of monosomy X, which turned out to be a mosaic with a monosomy X in 30% of cells in the direct preparation of amniotic fluid. From the NIPT provider, who interrogated all chromosomes, only 2/10 (20%) cases affecting other chromosomes could be partially confirmed. These were a case of trisomy 22 confirmed in 8% of native amniocytes (12/151) and a case of trisomy 17, which was found in a single clone (3.8% of analyzed clones) in amniotic fluid, only. Cases not confirmed were one trisomy 7, one trisomy 2, one trisomy 16, one trisomy 17, one monosomy 21, one combined case of a monosomy X and a trisomy 12, one case with a duplication 16p13.12-p12.3 and one case with a duplication 17q24.3q25.1. From the NIPT provider, who screened for the most common microdeletions 0/1 case was not confirmed (microdeletion 22q11.2). All cases not confirmed were normal.

Of note, two of the patients with positive NIPT findings but normal cytogenetics had repetitive NIPT: the first patient had three tests, of which the first two gave no result due to fetal fraction <5% and the third was indicative of Klinefelter-syndrome. The second patient had two NIPTs both indicative of monosomy X. We did not perform follow-up studies on the placenta or on maternal blood for any of those cases due to lack of material.

Problems observed with NIPT

Inconclusive or false NIPT results leading to a delayed diagnosis

We received material from three inconclusive NIPT cases. In the first case, we observed a triploidy by karyotyping in a spontaneous abortion, which occurred at 15 weeks of gestation. NIPT had been repeated twice using a test, which claims to detect triploidies, but had remained inconclusive. However, we did not perform additional investigations in order to characterize the triploidy as diandric or digynic and we have no information on the fetal fraction. The second prenatal case was a full trisomy 21, for which NIPT performed twice had been inconclusive. Of note, the woman was overweight and the fetal fraction might have been too low, which could explain inconclusive NIPT. In the third case the inconclusive NIPT result was not followed by any invasive testing and a baby with a trisomy 21 was born.

A further case with increased risk indicated by MSS in the first trimester was heavily delayed until diagnosis due to the misleading results of NIPT (Case 1): MSS indicated an increased risk for trisomy 13 and 18 (1:118). Subsequent NIPT indicated trisomy 21 in the 16th week of gestation. Amniocentesis with FISH testing on uncultured nuclei revealed two normal signals for the Down-syndrome critical region probe (LSI 21q22.13, control probe 13q14, Cytocell, UK) in 155 of 157 cells. Three cells showed three signals (1.9%). Thereafter, CMA and karyotyping from cultured amniocytes revealed a complex rearrangement indicative of chromoanasynthesis [12] affecting the chromosome 21 (Fig. 1). Of note, the Down syndrome critical region was not involved in the rearrangement and was present in two copies. A similar monosomy was described in the DECIPHER database in a child with microcephaly, ventriculomegaly, agenesis of the corpus callosum, deafness, dysmorphism and global developmental delay (case 285987). In light of these findings ultrasound investigation confirmed the fetal growth retardation, the ventricular septal defect, the cerebellar hypoplasia, absence of cavum septum pellucidum, abnormal movements and led to termination of pregnancy at the 20th week of gestation.

Insufficient resolution of NIPT-microdeletion

Case 2: First-trimester fetal ultrasound and MSS were normal. NIPT of a provider, which claims to detect the most common microaberrations, including the one described here, resulted normal at the 13th week of gestation. Fetal ultrasound at the 18th week revealed intrauterine growth retardation (IUGR) and amniocentesis was performed. FISH rapid test on uncultured amniocytes and conventional karyotype were normal, while CMA revealed a *de novo* terminal microdeletion of 1.2 Mb on chromosome 1pter-p36.33. Monosomy 1p36 is one of the most common terminal microaberrations and is a well-known syndrome characterized by dysmorphism, microcephaly, autism, intellectual disability, epilepsy, muscular hypotonia and growth retardation [13]. The parents decided to terminate the pregnancy immediately (21st week of gestation). Although the deletion observed in this fetus was below the technical resolution claimed by the NIPT provider, the relevance of the limited resolution may be underestimated by customers.

Delivery of severely affected babies with large chromosomal imbalances

We observed four cases, in which severely affected children were born and diagnosed right after birth with very large chromosomal imbalances, which were detected by conventional karyotyping alone. In all of these cases the couples were very upset because they had been counseled toward NIPT after abnormal ultrasound findings on routine pregnancy controls. No additional tests were performed, since all couples were reassured following

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