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Social and medical need for whole genome high resolution NIPT

Malgorzata I. Srebniak[1] | Maarten F. C. M. Knapen[2] | Lutgarde C. P. Govaerts[1] | Marike Polak[3] | Marieke Joosten[1] | Karin E. M. Diderich[1] | Laura J. C. M. van Zutven[1] | Krista A. K. E. Prinsen[2] | Sam Riedijk[1] | Attie T. J. I. Go[2] | Robert-Jan H. Galjaard[1] | Lies H. Hoefsloot[1] | Diane Van Opstal[1]

[1]Department of Clinical Genetics, Erasmus MC, Rotterdam, the Netherlands

[2]Department of Obstetrics and Fetal Medicine, Erasmus MC, Rotterdam, the Netherlands

[3]Institute of Psychology, Erasmus University Rotterdam, Rotterdam, the Netherlands

Correspondence
Malgorzata I. Srebniak, Department of Clinical Genetics, Erasmus MC, Rotterdam, the Netherlands.
Email: m.srebniak@erasmusmc.nl

Abstract

Background: Two technological innovations in the last decade significantly influenced the diagnostic yield of prenatal cytogenetic testing: genomic microarray allowing high resolution analysis and noninvasive prenatal testing (NIPT) focusing on aneuploidy. To anticipate future trends in prenatal screening and diagnosis, we evaluated the number of invasive tests in our center and the number of aberrant cases diagnosed in the last decade.

Methods: We retrospectively analyzed fetal chromosomal aberrations diagnosed in 2009–2018 in 8,608 pregnancies without ultrasound anomalies.

Results: The introduction of NIPT as the first-tier test led to a substantial decrease in the number of invasive tests and a substantially increased diagnostic yield of aneuploidies in the first trimester. However, we have also noted a decreased detection of submicroscopic aberrations, since the number of invasive tests substantially decreased. We have observed that pregnant women were interested in broader scope of prenatal screening and diagnosis than detection of common trisomies.

Conclusion: Since the frequency of syndromic disorders caused by microdeletions/microduplications is substantial and current routine NIPT and ultrasound investigations are not able to detect them, we suggest that a noninvasive test with resolution comparable to microarrays should be developed, which will also meet patient's needs.

KEYWORDS

diagnostic yield, microarray, NIPT, patients preferences, prenatal diagnosis

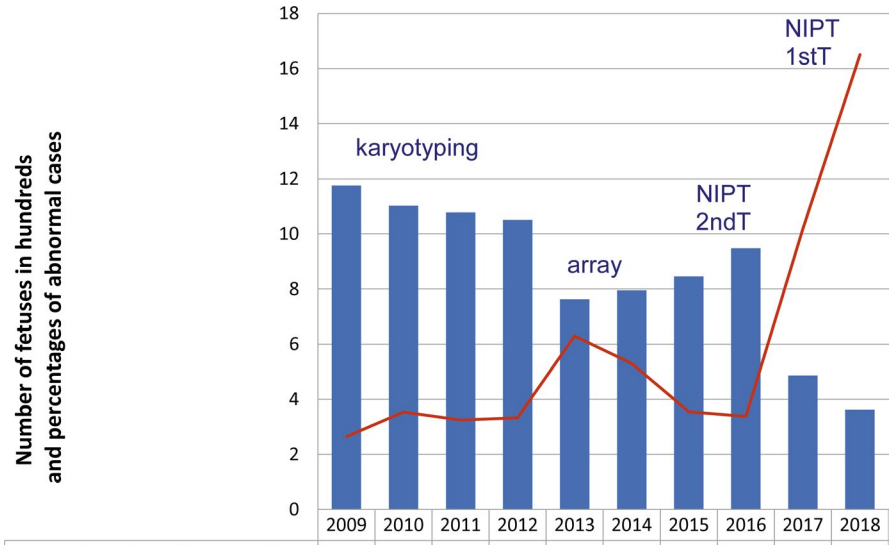
Technological innovations in the last decade significantly influenced the diagnostic yield of prenatal cytogenetic testing. This impact mostly depends on the testing resolution (Srebniak et al., 2017). In fetuses without ultrasound anomalies at the time of sampling (referred due to advanced maternal age [AMA], abnormal first trimester combined test [ftCT] results [with nuchal translucency, NT <3.5 mm], recurrence risk for chromosome aberrations), we, as others, previously showed that the replacement of karyotyping by microarray (in our clinic in 2012) led to a higher yield of pathogenic chromosome aberrations (Srebniak et al., 2017; Van Opstal et al., 2015; Vogel et al., 2018; Wapner et al., 2012). Moreover, our group showed that the majority of pregnant women opted for maximal information when applying for invasive testing

(Srebniak et al., 2011; van der Steen et al., 2015). In 2014, the introduction of genome-wide noninvasive prenatal testing (NIPT) in the Netherlands as an alternative for invasive testing in a high risk population (abnormal ftCT >1:200, previous child with trisomy), led to a decreased diagnostic yield in the test population in our region (Srebniak et al., 2017). This decrease was mostly caused by an inherent prenatal underdetection of submicroscopic aberrations, since the vast majority of pregnant women preferred NIPT (with limited resolution of ~15–20 Mb) over invasive diagnostic testing (resolution ~500 kb) (Van Opstal et al., 2015). Concerns on this underdetection of chromosome aberrations were also noted by Evans, Andriole, et al., (2018) and Evans, Evans, Bennett, & Wapner, (2018).

We have seen that the noninvasive character of NIPT has a tremendous psychological impact on pregnant women. More patients with high risk results after ftCT were willing to undergo follow-up investigations after NIPT was introduced than when only invasive testing was available. Because after introduction of NIPT in high risk pregnancies (with abnormal ftCT results) a decrease of diagnostic yield was noticed, we have previously concluded that NIPT should not be offered as second-tier screening test (Srebniak et al., 2017). Since 2017, NIPT as a first-tier screening test is available for every pregnant women in the Netherlands in the TRIDENT2 study (van der Meij et al., 2019). Following our previous study (Srebniak et al., 2017), we also wanted to investigate the effect of this major change in the national screening program on the overall diagnostic yield in our region, where we routinely offer microarray for cytogenetic investigations of chorionic villi and amniotic fluid. To achieve that, we analyzed the frequency of fetal chromosomal aberrations diagnosed in our laboratory in the time period 2009–2018 in 8,608 pregnancies. These were pregnancies without fetal ultrasound anomalies at the time of sampling, that were referred for invasive prenatal microarray testing due to AMA, abnormal ftCT (with NT <3.5 mm), recurrence risk for chromosome aberrations or abnormal NIPT results. We evaluated not only the number of aberrant cases, but also the number of invasive tests in our center. Such evaluations are indispensable to anticipate future trends in prenatal screening and diagnosis. The retrospective analysis method and exclusion criteria were used as described before (Srebniak et al., 2017).

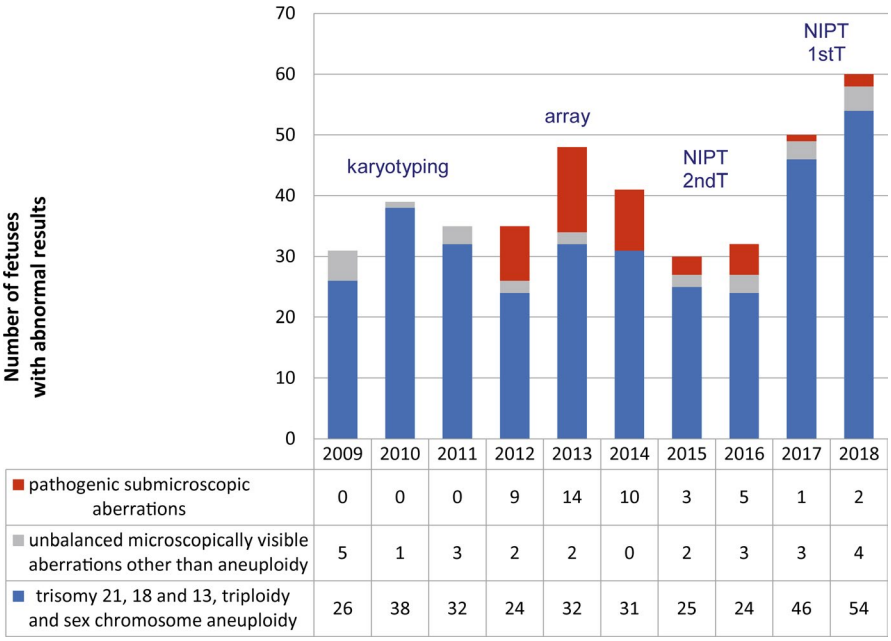
Evaluation of the influence of NIPT as a first-tier screening test and future perspectives: The introduction of NIPT as the first-tier test in our region led to the following.

1. A substantial decrease of the number of invasive tests in pregnant women without fetal ultrasound anomalies: from 1,176 in 2009 (AMA >35 year or abnormal ftCT), to 846 (2015, after introduction of NIPT as a second tier test and after abolishment of AMA as indication for prenatal diagnosis) and further down to 363 in 2018 (after introduction of NIPT as a first tier screening) (Figure 1).
2. In contrast to the previous study (Srebniak et al., 2017), a substantially increased diagnostic yield of pathogenic fetal chromosomal aberrations (Figures 1 and 2) in the first trimester was noted. The observed increase mainly involved the common aneuploidies (Figure 2).
3. However, it was noted that the total number of trisomy 21 cases diagnosed per year in *all* tested pregnancies (with or without ultrasound anomalies) still did not notably change, most probably due to the fact that uptake for



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
total number of fetuses without ultrasound anomalies tested (in hundreds)	11,76	11,02	10,78	10,51	7,63	7,95	8,46	9,48	4,87	3,63
% of abnormal cases	2,64	3,54	3,25	3,33	6,3	5,3	3,55	3,38	10,2	16,5

FIGURE 1 The number of fetuses without ultrasound anomalies (at the time of sampling) that were referred for invasive prenatal testing (amniocentesis or chorionic villi biopsy) and the percentage of aberrant cases in 2009–2018. The different settings are indicated: karyotyping, array, NIPT 2ndT—NIPT as a second screening test, NIPT 1stT—NIPT as a first screening test. The introduction of NIPT as a first tier screening test led to substantial decrease in the number of invasive tests. NIPT, noninvasive prenatal testing



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
pathogenic submicroscopic aberrations	0	0	0	9	14	10	3	5	1	2
unbalanced microscopically visible aberrations other than aneuploidy	5	1	3	2	2	0	2	3	3	4
trisomy 21, 18 and 13, triploidy and sex chromosome aneuploidy	26	38	32	24	32	31	25	24	46	54

FIGURE 2 Type of chromosomal aberrations detected in fetuses without ultrasound anomalies (at the time of sampling) referred for cytogenetic testing in 2009–2018 due to AMA (advanced maternal age), abnormal ftCT (first trimester combined test with NT <3.5 mm), recurrence risk for chromosome aberrations or abnormal NIPT results. AMA, advanced maternal age; ftCT, first trimester combined test; NIPT, noninvasive prenatal testing; NT, nuchal translucency

prenatal screening/testing did not increase with the introduction of NIPT.

4. We have noted a further decreased detection of submicroscopic aberrations (Figure 2), since the number of invasive tests substantially decreased and current NIPT resolution in our laboratory is still limited to ~15–20 Mb, enabling the detection of microscopically visible chromosome aberrations, but missing the submicroscopic ones. Moreover, detection is limited to autosomal chromosome aberrations.

From this study, we may conclude that the current prenatal screening program in the Netherlands is effective for common trisomies in our region, because it reduces the number of invasive testing, increases the efficiency of invasive prenatal testing and maintains the diagnostic yield of Down syndrome cases. Unfortunately due to limited NIPT resolution, it also shows that microdeletions/microduplications to a large extent will remain undiagnosed prenatally, and we previously showed that these disorders are unlikely to be detected by ultrasound examination (Srebniak et al., 2018). It is concerning as their incidence is rather high: 1:270, which is much higher than the prevalence of Down syndrome in younger women (Srebniak et al., 2018).

Our research data also showed that pregnant women are highly interested in more than screening for common aneuploidies, but are not willing to opt for invasive testing due to the risk for a miscarriage (van der Steen, 2019). This is also supported by the Dutch TRIDENT 2 study that showed that the majority (ca. 80%) of pregnant couples chooses whole genome testing instead of targeted testing of the common trisomies (van der Meij et al., 2019).

In conclusion, since the frequency of syndromic disorders caused by microdeletions/microduplications is substantial and because current prenatal screening protocols with NIPT focusing on aneuploidies and ultrasound investigations are not able to detect them, we suggest that a noninvasive test (either cfDNA [Fiorentino et al., 2017] or cell-based [Vossaert et al., 2018]) with resolution comparable to microarrays should be developed, which will also meet patient's needs.

CONFLICT OF INTEREST

All authors declare no conflict of interests.

ORCID

Malgorzata I. Srebniak https://orcid.org/0000-0003-3429-6156

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