CHAPTER 9

Non-invasive prenatal diagnosis for Down syndrome: no paradigm shift, just better testing. . . and it is already here!

We read with great interest the Opinion, 'Non-invasive prenatal diagnosis for Down syndrome: the paradigm will shift, but slowly', by Benn et al. published in the January issue of *Ultrasound in Obstetrics & Gynecology*.[1] We agree with the authors that techniques using cell-free fetal DNA in maternal plasma have great potential to improve public health and to expand reproductive choices of pregnant women. We also agree that before new tests can be introduced into clinical care, well-designed adequately powered prospective studies need to be performed. We were quite surprised, however, by a number of their negative remarks about this technology. We would like to address these, to provide an alternative view. This test is already available for pregnant women in an increasing number of countries. Thus, the test is already here!

Non-invasive prenatal testing (NIPT) for fetal trisomy: missing other diagnoses?

In many countries worldwide, pregnant women have been offered screening for fetal trisomy 21 (T21) for decades. The accepted program is first to inform women about the disease and their individual risk for T21, then to offer a sensitive screening test to select a high-risk group. This group is allowed to undergo an invasive test with karyotyping, which has a (near-) 100% accuracy to detect or exclude T21. With karyotyping, other chromosomal rearrangements, if present, are also detected. These coincidental findings are often regarded as useful, but can also be confusing, unexpected and unclear. Karyotyping is now often replaced by rapid aneuploidy detection: faster and cheaper, and logical given the fact that the woman was counseled about T21 specifically and screened using a test designed for T21. With the introduction of NIPT, we should not repeat the discussion on the estimated, really small (1:1600 to 1:4000) risk of, by abandoning full karyotyping, missing a clinically relevant anomaly that is undetectable by ultrasound. The true risk of missing such an anomaly on a population basis is actually 10–20 times lower, since it only applies to the 5% of women in whom we perform invasive testing. If we truly want to offer testing for chromosomal rearrangements and microdeletion/duplication syndromes, we should offer amniocentesis to all pregnant women, not only to the 5% who are screen-positive for T21. Even then, we would 'miss' hundreds of rare diseases, for which no genetic or ultrasound diagnosis is currently possible.

NIPT for fetal trisomy: screening or diagnosis?

Whether a test is diagnostic or for screening is not related to its accuracy. Many diagnostic tests have a far lower sensitivity and specificity than 99%. Screening involves offering a test to a population without a known increased risk, while diagnostic testing is done in patients with symptoms or a known high risk. The issue usually at the root of the 'diagnostic or not' debate is whether a positive NIPT result should be followed by a confirmatory invasive test.

The answer, at least for the coming years, is yes. Even with a specificity of 99.7%, in a general population with a prevalence of T21 of 1:500 (Dutch population), the positive predictive value is only around 60%.

Are there really disadvantages of NIPT?

NIPT would lead to a major reduction (around 75%) in invasive testing. NIPT now seems to work well in twins too; even if this were not the case, why would this be a reason not to offer NIPT to the 99% of women bearing singletons?[3] The equally rare confined placental mosaicism, where in 90% of cases the fetus is normal, is an interesting phenomenon to study, but would only very marginally increase the false-positive rate, and is no reason not to offer NIPT.

NIPT as first-line test or only for 'high-risk' women?

Offering NIPT as a first-line test to all pregnant women would have major advantages over current screening: not only reducing iatrogenic miscarriages of wanted, healthy children but also practically eliminating false reassurance. The current program as used in many countries (not modeling, but in the real world) results in the unexpected birth, *in women that were screened*, of a T21 child in one or two per 10 T21 cases. In addition, many women would like to know about T21 but decline what they see as the complex and uncertain serum and nuchal translucency (NT) testing, fear invasive testing, or are too late in the pregnancy for the first-trimester combined test. The only way to allow women to truly make an informed choice would be to offer a highly reliable, easy-to-explain and safe test. All that needs to be implemented, from the patient's and clinician's perspective, is adaptation of the content of counseling and arrangement of logistics to send a blood sample to a laboratory capable of performing this technology.

We do of course acknowledge the complex and highly sophisticated laboratory and biostatistical work behind NIPT. The only current restriction for offering it to all pregnant women would be cost, which will decrease with increasing numbers, advancing technology and more efficient methods, such as targeted testing.[4]

Counseling

In contrast to the current counseling on risk assessment with serum markers and NT measurement, everyone understands NIPT within minutes, including the absence of 100% certainty. This leaves time for a more in-depth discussion about T21, and whether parents are willing to accept a child with Down syndrome.

Will NIPT for trisomy replace the 11–14-week scan?

NT measurement was invented to screen for T21. Detailed first-trimester ultrasound by well-trained sonographers enables assessment of many functional and anatomical features of the fetus. Whether NT measurement will remain a cost-effective enterprise needs to be re-evaluated.

Conclusion

Finally, after decades of research, non-invasive prenatal trisomy testing is now a clinical reality. NIPT provides many advantages over current screening options. Organizational, financial and logistic aspects need to be solved. Introduction should be done after well-designed prospective clinical studies showing that expectations are truly met. NIPT is already here, and it will be increasingly hard to explain to the pregnant women under our care why we are not yet offering them this option.

REFERENCES

1. Benn P, Cuckle H, Pergament E. Non-invasive prenatal diagnosis for Down syndrome: the paradigm will shift, but slowly. Ultrasound Obstet Gynecol 2012;39:127–130.
2. Palomaki GE, Kloza EM, Lambert-Messerlian GM et al. DNA sequencing of maternal plasma to detect Down syndrome: an international clinical validation study. Genet Med 2011;13: 913–920.
3. Canick JA, Kloza EM, Lambert-Messerlian GM et al. DNA sequencing of maternal plasma to identify Down syndrome and other trisomies in multiple gestations. Prenat Diagn 2012;32: 730–734.
4. Norton ME, Brar H, Weiss J et al. Non-Invasive chromosomal Evaluation (NICE) Study: results of a multicenter, prospective, cohort study for detection of fetal trisomy 21 and trisomy 18. Am J Obstet Gynecol 2012;207:137.e1–8.