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Non-invasive prenatal diagnosis for aneuploidy: toward an integral ethical assessment

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ABSTRACT: The great promise of the pending introduction of non-invasive prenatal diagnosis (NIPD) for trisomy 21 (18 and 13) is that it enables one-step, early and safe testing for these abnormalities. The ethical debate so far has been limited to possible drawbacks of routine access to this type of testing: normalization of testing and abortion and adverse effects on autonomous decision-making. We address the ethical implications of the fact that routine NIPD affects the scope and strategy of current prenatal screening cascades. A decision is needed whether complementary (invasive) testing remains in place in order to avoid a loss of information as compared with current practice. If so, the supposed advantages of NIPD may be less significant than generally assumed. Accumulation of tests challenges informed consent and proportionality. Therefore, an ethical evaluation of the implications of NIPD for the prenatal screening strategy as a whole is needed.

Key words: ethics / cell-free fetal DNA / RNA / non-invasive prenatal diagnosis / aneuploidy / prenatal screening

Introduction

Screening for aneuploidies in the developed, primarily Western, world generally consists of two stages: (i) a risk assessment for trisomies 21 (Down's syndrome), 18 (Edward's syndrome) and 13 (Patau's syndrome), based on the combination of maternal serum testing, fetal nuchal translucency (NT) measurement and/or maternal age; (ii) a diagnostic follow-up test in case of an increased risk, performed on material obtained through invasive procedures: amniocentesis (AC) or chorionic villus sampling (CVS) (Bui and Meiner, 2008; Saller and Canick, 2008). Trials with non-invasive prenatal diagnosis (NIPD) using cell-free fetal DNA and RNA in maternal blood are currently performed worldwide and focus primarily on NIPD for trisomy 21, although trisomies 18 and 13 may follow (Chiu *et al.*, 2011; Ehrich *et al.*, 2011; Papageorgiou *et al.*, 2011). As a result, the current two-step testing may be replaced by a one-step diagnostic test targeted at these specific abnormalities (Go *et al.*, 2011).

Although there has been some ethical debate about this prospect, the discussion has concentrated mainly on NIPD itself and on possible implications of routine access to one-step, early, easy and risk-free prenatal diagnosis. The issues discussed include the perceived risk of normalization of testing and abortion, the fact that non-medical applications such as testing for fetal sex and paternity will become more easily available, and a possible negative effect on autonomous decision-making (Benn and Chapman, 2009; Schmitz *et al.*, 2009). Although these issues need to be addressed as well, we assert that the expected introduction of routine NIPD testing for trisomy 21 (and 18 and 13) urgently calls for ethical reflection on the overall scope and strategy of prenatal screening. A decision is needed whether complementary (invasive) testing remains in place in order to avoid a loss of information as compared with current practice. We discuss the practical and ethical implications of routine NIPD testing either for trisomy 21 only or for trisomies 21, 18 and 13.

Timing of NIPD-testing

Fetal DNA can be detected from 5 weeks of gestation and reliable NIPD may be feasible from 7 to 9 weeks of gestation (Wright and Burton, 2009). Therefore, it has been assumed in the literature that NIPD will take place rather early in the first trimester. This would

have the advantage that test results are received early, leaving more time for decision-making. Furthermore, possible termination of pregnancy in case of an adverse test result at this stage of pregnancy may be emotionally less burdensome than in the current approach, where diagnostic results are available after 11–14 weeks (CVS) or 16–20 weeks (AC) of gestation. Early testing is favourable from an ethical point of view as well. According to the dominant account, the moral status of the embryo/fetus is relatively low at the start and increases with further stages of development (the gradualist view) (de Wert, 1999). This notion of a gradually increasing moral status implies that selective abortion early in pregnancy is morally different from termination of affected pregnancies later in the first trimester or in the second trimester.

However, a serious disadvantage of early NIPD is that it may increase the burden of choice for women, since abnormal fetuses will be identified that would have miscarried spontaneously later in pregnancy (Wright, 2009). Moreover, the timing of an NIPD test offer will depend on how NIPD can best be integrated in the overall screening strategy.

Complementary testing: trisomies 18, 13 and NT measurement?

A possible scenario is that NIPD will initially be introduced for diagnosing trisomy 21 only and replace current two-step testing for this abnormality. This would maximize the benefits of NIPD at an early stage of embryo development: the drawbacks of false-positive and false-negative results generated by current risk assessment and the miscarriage risk attached to current invasive diagnostic methods would thereby be avoided (de Jong *et al.*, 2010; Go *et al.*, 2011). A recent study by Susman *et al.* (2010) suggests that this procedure would lead to 84% fewer invasive procedures, while diagnosing an additional 7% of trisomy 21 cases (corresponding with the false negatives in current risk assessment). However, this procedure would also imply that about 50% of chromosomal abnormalities other than trisomy 21, including trisomies 18 and 13, would be missed even when follow-up detection by the mid-trimester fetal anomaly scan is included (Benn and Chapman, 2010; Susman *et al.*, 2010). So to prevent testing being less informative than current practice, a solution would be to leave risk assessment and invasive diagnostic testing in place as a complementary screening trajectory for trisomies 18 and 13. Of course, the need for this does not arise as soon as these trisomies can be included in the NIPD array.

Abolishing current risk assessment raises a similar question with regard to NT measurement. Although offered as part of risk assessment for common aneuploidies, this procedure may concurrently lead to the early identification of pregnancies at a high risk of both chromosomal and non-chromosomal disorders, such as congenital heart defects and Mendelian disorders such as Noonan syndrome (Sonek, 2007; Bilardo *et al.*, 2010). Assuming that this information has added value in terms of reproductive options, the question arises what to do with NT measurement when introducing NIPD for the three trisomies. Should NT measurement be left in place as a separate screening test, complementary to NIPD? That would have the benefit of avoiding a reduction of the scope of prenatal screening and of the reproductive options that it is meant to provide. It would then only be logical to also offer this separate NT measurement to women who are currently not having risk assessment testing for common aneuploidies or who do not opt for NIPD in the future. However, separate NT testing must also be in line with the requirements of proportionality and informed consent.

Proportionality and informed consent

First, offering complementary testing comes at the price of confronting women with additional test offers shortly after NIPD has been performed. This may add to the burden of testing, because screening will increasingly become fragmented, leading to a series of moments of choice for women and possibly to a prolonged period of anxiety. To avoid this possible drawback of successive testing, NIPD and complementary tests could be offered simultaneously at weeks 11–12 of gestation, which is the usual period for risk assessment and gives the best performance for the NT measurement (Bilardo *et al.*, 2010). From a logistic point of view, such a combination would also be advantageous. However, it may be challenging to adequately inform women about those simultaneous, but very different test offers. A targeted diagnostic test for trisomy 21, a risk assessment test for trisomies 18 and 13, and NT measurement for a broad range of abnormalities are very dissimilar in kind and scope. They also differ with regard to the kind of test outcomes (risk versus diagnosis) and decision-making consequences (follow-up testing versus termination/continuation of pregnancy). Furthermore, this 3-fold combination of tests would diminish the advantages of a 'stand-alone' NIPD as the moment of testing would be delayed. In contrast to the promise of more simple counselling as a result of the conceptually easy character of NIPD (Wright, 2009), counselling would in fact become more complicated because of the heterogeneity of this compound test offer. Although NIPD would still have the advantage of being safe to perform, the other supposed advantages (early, easy) would, in this scheme, be less significant than generally assumed.

Second, since prenatal screening also requires the just use of scarce financial resources (distributive justice), the detection/cost ratio of NIPD for trisomy 21 or for trisomies 21, 18 and 13 with or without specific complementary testing has to be considered as well. A cost-effectiveness analysis should take into account all the relevant aspects of the test options, including costs for counselling, for follow-up testing and for the lifetime provision of care for people with abnormalities undetected by a stand-alone NIPD.

Third, the advantages of possible additional invasive testing for trisomies 18 and 13 may not evidently outweigh the disadvantages for participants, because its very limited target would negatively affect the detection/miscarriage ratio (Health Council of the Netherlands, 2001).

Fourth, separate NT measurement would amount to turning current 'incidental' findings into a screening target and require that informed consent be adapted accordingly. Presently, the possibility of those 'incidental' (non-aneuploidy-related) findings is not always included in pre-test information (Bilardo *et al.*, 2010). As a consequence, pregnant women may be confronted with findings that they were not prepared for and that they might otherwise have indicated that they did not want to receive (de Wert and Dondorp, 2006). It

is evident that pre-test information will have to cover these findings should NT measurement become a separate test. But given that an enlarged NT (≥3.5 mm) may indicate a risk for a wide range of abnormalities, this will not be possible on the level of specific abnormalities. As a form of more 'generic consent' (Elias and Annas, 1994) seems unavoidable here, the challenge is to offer not too much but yet enough information to enable women's informed decision-making with regard to this testing.

Conclusion

The general opinion is that NIPD holds great promise to enable prenatal diagnostic testing earlier in pregnancy and in a one-step, easy and safe manner. However, as our ethical considerations of the pending introduction of NIPD for trisomy 21 (and then 18 and 13) suggest these expectations may well reflect a one-sided view that overlooks the broader context of prenatal screening in which NIPD has to be implemented. A decision is needed whether only NIPD or NIPD and complementary testing will be offered. This requires a proactive ethical evaluation to find out which approach is most in line with the principles of respect for autonomy and of beneficence, underlying the normative framework for prenatal screening.

Authors' roles

The first draft of this article was conceived by A.J., W.D. and G.W. C.D. and S.F. had a role in supplying further clinical information and critical revision.

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References

Benn PA, Chapman AR. Practical and ethical considerations of noninvasive prenatal diagnosis. *JAMA* 2009;**301**:2154–2156.

Benn PA, Chapman AR. Ethical challenges in providing noninvasive prenatal diagnosis. *Curr Opin Obstetr Gynecol* 2010;**22**:128–134.

Bilardo C, Timmerman E, Pajkrt E, van Maarle M. Increased nuchal translucency in euploid fetuses-what should we be telling the parents? *Prenat Diagn* 2010;**30**:93–102.

Bui T-H, Meiner V. State of the art in prenatal diagnosis. In: Leuzinger-Bohleber M, Engels E-M, Tsiantis J (eds). *The Janus Face of Prenatal Diagnostics. A European Study Bridging Ethics, Psycholanalysis, and Medicine*. London: Karnac Books, 2008,61–86.

Chiu R, Akolekar R, Zheng Y, Leung T, Sun H, Chan K, Lun F, Go A, Lau E, To W *et al*. Non-invasive prenatal assessment of trisomy 21 by multiplexed maternal plasma DNA sequencing: large scale validity study. *BMJ* 2011;**342**:c7401.

de Jong A, Dondorp W, de Die-Smulders C, Frints S, de Wert G. Non-invasive prenatal testing: ethical issues explored. *Eur J Hum Genet* 2010;**18**:272–277.

de Wert G. Looking ahead. Reproductive technologies, genetics and ethics. Thela Thesis. Amsterdam, 1999.

de Wert G, Dondorp W. Ethical issues. In: van Vugt M, Shulman K (eds). *Prenatal Medicine*. New York/London: Taylor & Francis, 2006;575–604.

Ehrich M, Deciu C, Zwiefelhofer T, Tynan J, Cagasan L, Roger T, Lu V, McCullough R, McCarthy E, Nygren A *et al*. Noninvasive detection of fetal trisomy 21 by sequencing of DNA in maternal blood: a study in a clinical setting. *Am J Obstet Gynecol* 2011;**204**:205.e1–11.

Elias S, Annas G. Generic consent for genetic screening. *N Engl J Med* 1994;**330**:1611–1613.

Go AT, van Vugt JM, Oudejans CB. Non-invasive aneuploidy detection using free fetal DNA and RNA in maternal plasma: recent progress and future possibilities. *Hum Reprod Update* 2011;**17**:372–382.

Health Council of the Netherlands. Prenatal screening: Down's syndrome, neural tube defects, routine-ultrasonography. Publication no. 2001/11. The Hague: Health Council of the Netherlands, 2001. http://www.gezondheidsraad.nl/en/publications/prenatal-screening-down-s-syndrome-neural-tube-defects-routine-ultrasonography.

Papageorgiou EA, Karagrigoriou A, Tsaliki E, Velissariou V, Carter NP, Patsalis PC. Fetal-specific DNA methylation ratio permits noninvasive prenatal diagnosis of trisomy 21. *Nat Med* 2011;**17**:510–513.

Saller D, Canick J. Current methods of prenatal screening for Down syndrome and other fetal abnormalities. *Clin Obstetr Gynecol* 2008;**51**:24–36.

Schmitz D, Netzer C, Henn W. An offer you can't refuse? Ethical implications of non-invasive prenatal diagnosis. *Nat Rev Genet* 2009;**10**:515.

Sonek J. First trimester ultrasonography in screening and detection of fetal anomalies. *Am J Med Genet C Semin Med Genet* 2007;**145C**:45–61.

Susman M, Amor D, Muggli E, Jaques A, Halliday J. Using population-based data to predict the impact of introducing noninvasive prenatal diagnosis for Down syndrome. *Genet Med* 2010;**12**:298–303.

Wright C. Cell-free fetal nucleic acids for non-invasive prenatal diagnosis. Report of the UK expert working group: PHG Foundation. 2009. http://www.phgfoundation.org/reports/4985/.

Wright CF, Burton H. The use of cell-free fetal nucleic acids in maternal blood for non-invasive prenatal diagnosis. *Hum Reprod Update* 2009;**15**:139–151.