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Opinion

Counseling for non-invasive prenatal testing (NIPT): what pregnant women may want to know

Sequencing of cell-free fetal and maternal DNA fragments (cfDNA) in maternal plasma can be used to test for fetal chromosomal abnormalities. In particular, prediction of the presence or absence of fetal trisomy 21, the most common fetal chromosomal abnormality, has been proved to be highly accurate. The first studies, showing > 99% accuracy, were done in selected high-risk groups[1,2]. More recent studies in average-risk populations of pregnant women confirm, as was expected biologically, that the test works equally well in the general population[3–7]. Not surprisingly, this safe and accurate test, commonly referred to as non-invasive prenatal testing (NIPT), increasingly is being offered by clinicians and requested by pregnant women who want to be informed about the possibility of trisomy 21 in their unborn child.

With the first studies suggesting very high accuracy of trisomy 21 detection, there was hope that after decades of searching for this 'Holy Grail', a safe blood test could replace chorionic villus sampling and amniocentesis, eliminating (fear of) procedure-related miscarriages. From larger follow-up studies, we now know that while an NIPT result positive for trisomy 21 often means that the fetus is affected, this is not always the case, and therefore confirmation using an invasive test remains necessary, at least when the woman is considering an irreversible decision. Furthermore, sensitivity for detection of trisomy 21 is > 99% in practically all studies, but some missed cases have been reported. Thus, although highly accurate, NIPT is not perfect.

In the not-so-distant past, the use of maternal age alone to select women to undergo invasive testing was replaced by various forms of measuring maternal serum markers with or without nuchal translucency (NT) measurement. In countries in which this was implemented well, unnecessary invasive tests (and related miscarriages) significantly decreased, with concomitant improved detection, thus improving women's reproductive choices[8]. Still, the vast majority of invasive tests following screening for trisomy reveal a normal result, while the screening test is falsely reassuring in at least one in 10 pregnancies with a trisomy 21 fetus. The use of NIPT enables us to further improve the quality of prenatal testing for fetal abnormalities.

The aim of counseling a pregnant woman before she chooses to undergo any test which can have major consequences is to provide sufficient understanding of the test characteristics, limitations and risks for her to make what we call an 'informed choice' regarding whether she wants to undergo this test, another one or no test at all. The introduction of NIPT does not change this general principle. We have been counseling women of advanced maternal age on invasive testing for decades, and we are used to discussing serum- and NT-based screening, which, when all aspects of the various tests are to be explained, is quite a complex task. Following the first publications on NIPT for trisomy 21, clinicians for a while were under the impression that pretest counseling would become an easier, if not almost superfluous, task. A simple message ('If you want to know about trisomy 21, we take a tube of blood and let you know in a week or so whether your baby is affected.') was thought, at least by some, to be capable of replacing the complex explanation involving serum markers, the meaning of this rim of fluid in the baby's neck, an algorithm including the age of the mother and not so easy-to-understand reasons behind the cut-off between high and low risk.

However, with the increasing use of NIPT in clinical practice, there is a rising awareness among professionals and policy makers that adequate pre-test counseling is still important, even for NIPT, in order to prevent misconceptions, disappointments and, in some cases, inappropriate selection of this test by women or doctors.

In this Opinion paper, we describe what pregnant women may want to know about NIPT before consenting to undergo this test, and summarize useful aspects, which could be included in various forms of patient information (websites, guidelines, booklets or by personal contact in the clinic).

Precounseling assessment: history and ultrasound

Although, due to logistic or financial reasons, it is not applied universally, early sonographic confirmation of intrauterine pregnancy can be very helpful before discussing and planning any further testing in pregnancy. A brief history, including information about last menstrual period, mode of conception and previous pregnancies, is useful before performing this ultrasound examination. Women understandably appreciate seeing their fetus and its beating heart on ultrasound for the first time. After a quick confirmation of viability, dating and exclusion of a multiple pregnancy, which any obstetric caregiver can do using virtually any ultrasound machine, the remaining part of the visit will pass in a more relaxed atmosphere. Furthermore, missed miscarriages are common; their detection at the start of the clinic visit prevents time

being wasted on counseling for screening tests. Counseling will of course differ considerably with the diagnosis of twins or major structural abnormalities such as anencephaly.

This first 'dating' scan helps to time correctly the preferred screening tests, in particular gestational age-dependent serum/NT testing. NIPT should be done after 10 weeks' gestation, so a dating scan preceding blood sampling is useful.

Precounseling questions

Before providing the pregnant woman (and ideally her partner) with details on test options, it is worthwhile checking whether she is already knowledgeable on the topic (from previous pregnancies, websites, booklets) and whether she is at all interested in information concerning the health and possible anomalies of her fetus. Some women firmly state that they do not want to know such things until after birth, and may even feel insulted when the suggestion of screening and possible termination is made. In some societies, ethicists and policy makers emphasize this 'right not-to-know'.

General aspects of counseling for screening, diagnosis and intervention

'Screening' is a term generally used to describe testing in unselected, asymptomatic people, with the aim of timely selection of a limited subgroup at increased risk for a disorder, for which a reliable diagnostic test and a useful intervention are available. The screen-positive 'high-risk' subgroup may then be offered a final test to select those really requiring intervention. This final test, applied to actually diagnose the disease in question, is then called 'diagnostic'. The outcome after intervention should be improved compared with intervening only after the occurrence of clinical symptoms.

In many screening programs, the initial screen-positive subgroup does not undergo a final diagnostic test immediately, but is offered further selection, aimed at reducing the number of patients who will be subjected to treatment. In serial testing programs, doctors often use increasingly accurate but also more expensive, more risky or more painful tests, which they, or the policy makers, do not want to apply to the general population. The value of any screening test depends on the overall value of the screening–diagnosis–intervention program into which the test is incorporated. The best assessment of the clinical value of a single test is to compare a complete program including this test with a similar program that does not include the test.

In addition, the costs and benefits of a test vary considerably depending on at what point in the program the test is offered; e.g. a first-line test for everyone, or only for a subgroup, selected by another screening test first. Many argue that tests used in the stepwise selection process, before offering the final diagnostic test, should all be called 'screening tests'. This is debatable, since true screening implies, as argued above, the offering of tests to asymptomatic, low-risk, general populations. We seem to lack a fitting term for the 'intermediate' tests that are used to further narrow down the initial screen-positive group before applying the final diagnostic test. For now, it seems best to call only the final test, which identifies the patients eligible for intervention, the 'diagnostic test', with all other tests in the stepwise selection program being called 'screening tests'. As outlined above, NIPT is the best-performing screening test for trisomy 21. We need to determine in the near future whether NIPT is best used before, after or instead of currently used tests in a screening program, and this will depend mainly on cost and logistical issues, which are likely to vary between societies and healthcare systems. It is beyond the scope of this paper to discuss all options or to make recommendations.

Accuracy and positive predictive value

Often, test characteristics are described primarily by sensitivity and specificity, or the more intuitive terms, detection rate and false-positive rate. For the pregnant woman, translation of these figures is often needed, since she is interested mainly in the meaning for her of a positive or negative result: 'How sure can I be that my child does not have Down syndrome when the screening test is negative?' 'What are the odds of carrying an affected child when the screening test is positive?'

For all involved, the positive predictive value (PPV) is a valuable parameter. This tells us what percentage of fetuses is truly affected when the screening test is positive. Unlike sensitivity and specificity, the PPV is strongly dependent on the prevalence of the disease in the screened population. The currently used serum-/NT-based screening methods have a detection rate of 81–96% for a false-positive rate of 2–5%, while NIPT studies suggest detection rates of trisomy 21 of 98.6–100% for a 0–2.1% false-positive rate[8]. Even in one of the best-performing national programs for trisomy 21 (Denmark), only 92 of the 1704 invasive tests following a positive screening revealed trisomy 21 (PPV, 5.4%)[9]. When using NIPT in a low- or average-risk population, in 1365 blood samples Bianchi *et al.*[7] found nine positive NIPT results, of which five were confirmed trisomy 21 and four were normal, giving a PPV of 56%, ten-fold higher than that of serum/NT testing. The two important conclusions from such calculations are that: (1) NIPT shows superior performance over serum-/NT-based screening, and (2) the very high but not 100% specificity of NIPT means that, especially when applied in a low-prevalence population, confirmation by an invasive test remains necessary, since the PPV will be far from 100%.

General aspects of counseling for aneuploidy screening

Ideally, before subjecting any person to any medical test, the doctor would want to discuss the goal of the test, the benefits of having the information that the test provides, the limitations, the risks and the costs. In screening for

diseases, in the absence of known risk factors, the person to be tested may want to know something about the disease that is looked for: the chances of actually having the disease, as well as its severity, treatment options and the risks involved when screening is declined.

Often, however, doctors presume the patient to have at least basic knowledge of the disease itself (whatever it is, e.g. human immunodeficiency virus, cervical cancer, Down syndrome) or, at most, a leaflet is provided. In screening for fetal trisomy, one could leave until the post-test counseling session any discussion about what the disease means for the child itself and the family in terms of prognosis and treatment options, thus restricting it to the small minority that receives a screen-positive test result. However, if women are to be granted an informed choice to accept or decline screening, sufficient knowledge on the disease itself must be a prerequisite.

A common misconception, highly relevant when women have to choose between different test options, is that 'Down syndrome' encompasses most of the possible causes of mental disability in children. Although it is by far the most common chromosomal abnormality in live-born children in the Western world, the combined incidence of all rare diseases associated with neurodevelopmental delay is several times higher than the 1 in 500–700 of Down syndrome. To prevent this misconception, it would be advisable to verify some basic understanding about fetal trisomy, and the limitations of a reassuring test for this, before performing the test.

A second common misunderstanding about Down syndrome is the perceived limited severity of the disease. Many parents tell the counselor that they know what Down syndrome means, often based on quite exceptional cases of smiling young children they have seen in movies, in music bands and on television shows, some of whom are likely mosaics. Parents-to-be may benefit from having a realistic image, including knowledge of the unpredictable variation of physical and mental disability, specialized care needed, and the long-term prognosis of adults with Down syndrome.

The issues described thus far apply to all types of screening offered to pregnant women for fetal trisomy. When screening only by maternal age, explaining the test itself (how old are you?) is easy. The emphasis in this case might lie on the huge number of false positives and false negatives resulting from this option. The first-line tests most commonly offered currently are based on risk calculations using maternal age and two, three or four serum markers, with or without NT measurement between 11 and 14 weeks' gestation. These test characteristics are so much better compared with using age alone that, when this type of screening is available, the use of age alone is often discouraged. However, some women may elect not to accept the cut-off of 1 in 200 or 1 in 300 used to consider them 'low risk'; they may want to have optimal certainty that their fetus does not have Down syndrome and request an invasive test. In healthcare systems in which the women do have that choice, they require some comparative data on various tests before being able to make an 'informed choice'. This is particularly important to prevent serious disappointment, if not medicolegal issues, in those cases in which the (serum/NT) screening test gave a reassuring (risk < 1:300) result, but at birth the child was found to have Down syndrome.

Unexpected additional findings after invasive testing: benefit or burden?

Another issue that may affect a woman's choice, and a topic of debate in the fetal medicine world, is that the invasive test offered to screen-positive women not only detects fetal trisomy, but, depending on the laboratory technique used, can detect a number of other abnormalities. Some consider this a benefit, in particular for women who take the risk of having a miscarriage due to the invasive test, to provide as much information on fetal health as possible, while others state that the diagnostic test should only test what was screened for, since many of the rare additional findings are of unclear significance, causing anxiety and complex counseling problems. This issue is not new; traditional karyotyping has always occasionally revealed 47,XXX, marker chromosomes and mosaics, confusing doctors and patients, although sometimes, of course, clinically relevant additional findings do occur[10]. The now often-applied chromosomal microarray analysis (CMA), however, magnifies this issue. CMA enables detection of a huge range of anomalies with various degrees of severity, including many with variants of uncertain clinical significance[11]. In addition, CMA is often combined with DNA analysis of both parents, which may reveal unexpected variants or abnormalities in their genome. This entity may lead to challenging counseling issues, problematic for many counselors[12] and of course for parents.

Again, this issue is not related directly to the introduction of NIPT. However, given the greater accuracy of screening with the use of NIPT, the number of women actually undergoing chorionic villus sampling or amniocentesis will significantly decrease. This was, after all, a major goal of developing NIPT in the first place. Interestingly, some investigators now publish calculations on how many clinically significant abnormalities will be 'missed', with the improved selection for invasive testing thanks to NIPT[13]. This argument at least requires further discussion. Is it appropriate to highlight the benefits of finding additional anomalies using current screening tests, because more (invasive) diagnostic tests are performed due to the relatively high false-positive rate? We may need to reconsider the goals of prenatal screening for fetal anomalies, and re-evaluate the currently common restrictions in choices we offer to pregnant women. This discussion is beyond the scope of this article.

What may women want to know?

Not all pregnant women want to know all possible details about the various tests beforehand. Many, however, do ask questions; their doctors should have sufficient knowledge to answer most of these, and should be able to find

the information or refer to a colleague if they do not. Many programs have developed written and web-based decision-aids. With the introduction of NIPT, both the knowledge of doctors and the information in booklets and websites need to be updated. In Table 1, we summarize the most relevant questions for clinical practice, based on our collective experience of counseling for NIPT in the past several years, with answers provided in Appendix S1.

How to keep professionals updated?

Although it is every professional's own responsibility to have sufficient up-to-date knowledge, scientific societies or national boards may feel they should play an active role to promote and facilitate training in this area, in particular when they have issued statements to support the introduction of NIPT. Given the ongoing advances in this field, any list of questions and answers, or tables with specific performance data, will soon be outdated. One solution to assist professionals in staying up-to-date on everything a patient may want to know about NIPT is to actively maintain a dedicated, easy-access website with information on the latest developments. Ideally, such websites should be controlled by independent not-for-profit organizations, providing objective, scientifically sound, unbiased information. Perhaps international scientific societies such as ISUOG (the International Society of Ultrasound in Obstetrics and Gynecology), The FMF (Fetal Medicine Foundation) and ISPD (the International Society for Prenatal Diagnosis) may assist in keeping clinicians well informed on the advances in this exciting, rapidly changing field which holds tremendous promise for improved care of pregnant women.

Table 1 Frequently asked questions on screening for fetal trisomy and on non-invasive prenatal testing (NIPT)

- What are trisomies 21, 18 and 13?
- What are risks for these anomalies in general?
- What are the *a priori* risks for trisomy for this individual patient?
- In case of a fetal trisomy, what are the chances of spontaneous miscarriage/perinatal demise from time of testing onwards?
- What are the remaining risks for other major fetal anomalies when trisomies are excluded?
- What are the chances of detecting other fetal anomalies using (routine) ultrasound in the first and second trimesters?
- From what testing options can the pregnant woman choose?
- How accurate is each of these tests; what are the benefits, limitations and risks?
- What are the chances of a failed test, of the need for redraw and of an uninterpretable result?
- When is the result available?
- How is the result communicated (negative and positive, high/low probability, risk score)?
- What does it mean when the result is positive?
- What are the odds of being affected given a positive result?
- What are the options when the test is positive?
- What are the options when the diagnosis of trisomy is confirmed?
- What is the remaining risk for trisomy when NIPT is negative?
- Is the sex of the fetus tested, is the result communicated, and how reliable is this?
- Can other abnormalities besides trisomies 21, 18 and 13 be found by NIPT and, if so, will they be communicated?
- Can abnormalities in maternal DNA be detected and, if so, will they be communicated?

Answers are provided in Appendix S1.

Conclusion

In more than four decades of offering pregnant women testing for fetal trisomy 21, the accuracy and safety of screening and diagnosis programs have improved repeatedly, with ultimately the introduction of NIPT as a close to perfect screening test. As for currently used screening tests, it is reasonable to assume that both doctors and pregnant women may want to be well informed regarding its characteristics, benefits and limitations before making any decisions.

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D. Oepkes*†, Y. Yaron‡, P. Kozlowski§, M. J. Rego de Sousa¶, J. L. Bartha**, E. S. van den Akker††, S. M. Dornan‡‡, E. Krampl-Bettelheim§§, M. Schmid¶¶, M. Wielgos***, V. Cirigliano†††, G. C. Di Renzo‡‡‡, A. Cameron§§§, P. Calda¶¶¶ and A. Tabor****

*†Leiden University Medical Center, Department of Obstetrics, K-06-35, P.O.Box 9600, 2300 RC, Leiden, The Netherlands; ‡Prenatal Diagnosis Unit, Genetic Institute, Tel Aviv Sourasky Medical Center, Affiliated to Department of Obstetrics & Gynecology, Sackler Faculty of Medicine, Tel Aviv University, Israel; §Praenatal-Medizin und Genetik, Düsseldorf, Germany; ¶Immunology and Autoimmunity Unit, Department Clinical Pathology, Hospital Prof. Fernando Fonseca E.P.E., Amadora, Portugal; **Division of Obstetrics and Gynecology, University Hospital La Paz, Universidad Autónoma de Madrid, Madrid, Spain; ††Onze Lieve Vrouw Gasthuis, Amsterdam, The Netherlands; ‡‡Royal*

*Maternity Hospital, Belfast, UK; §§Medical University Vienna, Department of Obstetrics and Gynecology, Division of Obstetrics and Feto-Maternal Medicine, Vienna, Austria; ¶¶Department of Obstetrics and Feto-maternal Medicine, Medical University of Vienna, Vienna General Hospital, Vienna, Austria; ***1st Department of Obstetrics and Gynecology, Medical University of Warsaw, Warsaw, Poland; †††Unitat de Biologia, Departament de Biologia Cellular, Fisiologia i, Immunologia, Universitat Autònoma de Barcelona, Bellaterra, Barcelona, Spain; ‡‡‡Dept. of Ob/Gyn and Centre for Perinatal and Reproductive Medicine, Santa Maria della Misericordia University Hospital, San Sisto, Perugia, Italy; §§§The Ian Donald Fetal Medicine Centre, Southern General Hospital, Glasgow, UK; ¶¶¶The Fetal Medicine Center and Ultrasound Unit, Department of Obstetrics & Gynecology, First Faculty of Medicine, Charles University in Prague, Prague, Czech Republic; ****Rigshospitalet, Copenhagen University Hospital, Center for Fetal Medicine and Pregnancy, The Juliane Marie Center, Copenhagen, Denmark*
Correspondence.
(e-mail: d.oepkes@lumc.nl)

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Appendix S1 Answers to frequently asked questions on screening for fetal trisomy and on non-invasive prenatal testing