Executive summary

Health Council of the Netherlands. Population Screening Act: Non-Invasive Prenatal Test (NIPT) as initial test for Down's, Patau's and Edwards' syndrome. The Hague: Health Council of the Netherlands, 2016; publication no. 2016/10.

On behalf of the national NIPT consortium, VU University Medical Center Amsterdam (VUmc) has submitted a permit request for the use of a non-invasive prenatal test (NIPT) as the initial test in prenatal screening for Down's, Patau's, Edwards' syndromes (trisomy 21, 13 and 18). This is a study introduction in the form of a scientific study (TRIDENT-2). This study requires a permit under the Population Screening Act. The Health Council of the Netherlands' Committee on Population Screening is advising the Minister of Health, Welfare and Sport with regard to the granting of this permit.

The study

In the study, the applicant plans to investigate the introduction of NIPT as the initial screening test. In 2014, a study started into the use of NIPT in pregnant women who are at increased risk of a foetus with a trisomy. Following a positive combination test, they can first have a NIPT (TRIDENT-1), rather than immediately having an invasive test (chorionic villus sampling or amniocentesis). At the start of that particular study, too little was still known regarding the test characteristics of NIPT in pregnant women who were not at increased risk of a foetus with a trisomy 21, 13 and 18. Further research has now been carried out into this issue. When the new study starts, women who are interested in taking part in the screening can choose which initial test they would prefer, the

combined test or the NIPT. By means of questionnaires and interviews, the study will examine women's motives for deciding whether or not to participate in the screening and their reasons for opting for the combination test or the NIPT.

Assessing conformity with the legal requirements

To qualify for a permit, the study must meet the requirements of scientific rigour and those of the regulations governing medical practice. Furthermore, the benefits to the participants must outweigh the risks.

Scientific rigour

The Committee finds that the scientific rigour of using the NIPT as the initial screening test is sufficient. The test characteristics are favourable: NIPT misses very few abnormalities (for Down's syndrome, its sensitivity is 94.5 percent; for trisomy 13 and 18, it is 76,3 percent and 85,2 percent, respectively), and rarely produces an abnormal result in a foetus without one of the three trisomies (for Down's syndrome, its specificity is 99.9 percent, for trisomy 13 and 18, it is 99.9 percent and 99.8 percent, respectively).

Benefit-risk ratio

The benefit-risk ratio is favourable. NIPT offers significant advantages over the combined test. As it produces fewer false-positive results, invasive follow-up testing (chorionic villus sampling or amniocentesis) is less often required. As a result, the small risk of miscarriage due to invasive testing declines in relation to the number of abnormalities detected. Also, fewer women will be needlessly worried by a positive result which further testing subsequently will show to be incorrect. Furthermore, NIPT can be used from ten weeks after conception until the end of the pregnancy. On average, compared to the combination test pregnant women can also find out more quickly whether the foetus has trisomy 21, 13 or 18.

In NIPT, foetal DNA (from the placenta) that circulates in the blood of the pregnant woman is examined for evidence of foetal abnormalities. This does involve the possibility of incidental findings, i.e. additional findings in the foetus and the woman in question other than the chromosomal abnormalities primarily targeted by the test. Some of these findings can be avoided, by the use of an analysis filter. While some participating centres do use such a filter, others do not, as they suspect that it may adversely affect the quality of the test. The

Committee believes that, in principle, implementation in the Netherlands must be equal and that the approach with the smallest chance of incidental findings should be chosen. As yet, too little is known concerning the impact of analysis filters on quality. Accordingly, for the time being, the Committee considers it acceptable for both approaches (the targeted approach and the whole genome approach) to be used within the NIPT consortium. This is subject to the provision that research is carried out to determine the impact of filters on the quality of the NIPT, into the number and type of incidental findings involved, and on the impact these have on participants. This study is important for the way in which the prenatal screening programme will be organised in future.

Rules for medical practice

According to the Committee, the information provided about screening requires improvement. The differences between the various test options, as well as the benefits and risks involved, need to be made clear. Furthermore, those participating in the screening should be informed in advance about the chance of incidental findings, and the potential impact of this on the woman and the foetus. It is vital that the women involved are given the opportunity to indicate in advance that they do not wish to be informed about any incidental findings (the right not to know). The Committee believes that, in principle, information should only be provided about NIPT results relating to trisomy 21, 13 or 18 and about findings that indicate serious health risks for the woman in question, unless the woman has indicated that she also wishes to be informed about any other findings.

Recommendation

The Committee advises the Minister to grant the permit, subject to the following conditions:

- The applicant should conduct a scientific study into the impact of analysis filters on the quality of NIPT, into the number and type of incidental findings involved, and their impact on the participants. No such studies have yet been carried out, either at national or international level. In the future, this may be of considerable value in terms of the way in which the national prenatal screening programme is organised (or reorganised).
- A quality standard for the entire screening chain must be drawn up to ensure that all participating centres can be tested for compliance with predetermined quality requirements.

- The information for pregnant women will be modified to ensure that participants are fully informed about the benefits and risks of both the combination test and the NIPT, and about the steps they can take in the event of a positive combination test or NIPT. Furthermore, prior to the screening, the women should be informed about the chance of incidental findings relating to the foetus or to themselves, and about the potential significance and impact of such findings.
- The women's right not to know must be safeguarded. The Committee believes that incidental findings indicating the possible presence of a foetal abnormality should only be communicated to the pregnant woman in question if she has expressly indicated, in advance, that she wishes to be informed about such outcomes. If the pregnant woman in question has indicated that she does not wish to be informed about any incidental findings indicating that she might have a treatable disease, then her wish must be respected, unless the caregiver considers that the patient's interests or the interest of others, in not knowing, do not outweigh the drawbacks involved. This could be the case in the event of possible maternal cancer, as an incidental finding of NIPT.

The Committee further recommends that steps be taken to ensure that women do not – directly or indirectly – help to fund the cost of the study's questionnaires and interviews (via the price charged for the NIPT).