Executive summary

Health Council of the Netherlands. NIPT: dynamics and ethics of prenatal screening. The Hague: Health Council of the Netherlands, 2013; publication no. 2013/34.

In recent years, new tests have been developed to identify chromosomal abnormalities in fetuses, such as Down's syndrome. These tests are non-invasive, making use of fetal DNA found in the mother's blood, relevantly reducing the need for invasive investigations such as amniocentesis and chorionic villus sampling. The new tests represent not only a technical breakthrough, but also significant ethical relevance. To what degree do they result in improved screening, in perspective to the aim of 'providing meaningful reproductive choices' to the pregnant woman and her partner? This is one of the questions addressed by the Population Screening Committee of the Health Council in this monitoring report. The monitoring report is exploratory in nature and places the new non-invasive tests within wider developments in prenatal screening.

Current prenatal screening

Prenatal screening encompasses the array of medical tests that all pregnant women qualify for during pregnancy. This is distinct from tests that may be indicated for individual pregnant women, for example because a child with a specific abnormality has already been born in their family or to close relatives. The latter cases constitute an individual diagnostic process and not population based screening.

There are two main forms of prenatal screening: 1) screening for conditions that may lead to an unfavourable pregnancy outcome for which timely identification allows preventive intervention, and 2) screening for fetal abnormalities that may lead to a decision by the pregnant woman and her partner whether to carry the pregnancy to term or terminate it. The first form of screening pertains to infectious diseases and blood group antibodies; the second pertains to screening for Down's syndrome and other chromosomal abnormalities, as well as to screening for structural defects by the second trimester fetal anomaly scan (FAS).

Screening for Down's syndrome (trisomy 21) and other chromosomal abnormalities (trisomy 13 and 18) is a stepped procedure: the first step is a so-called combined test, which is performed at a pregnancy term of eleven to fourteen weeks. Pregnant women in whom the combined test indicates an elevated risk of a child with Down's syndrome (or trisomy 13 or 18) are offered follow-up testing to determine whether the fetus has indeed a chromosomal abnormality. This is done using amniocentesis (at fifteen to eighteen weeks) or chorionic villus sampling (at eleven to fourteen weeks). Data from the Netherlands show that the combination test identifies 85-95 percent of all pregnancies with trisomy 21 (sensitivity), with a specificity of 93-95 percent (5-7 percent false-positive results). Far fewer women make use of the combined test in the Netherlands than in other European countries; uptake is 27 percent here, compared to over 90 percent in Denmark, for example. Amniocentesis and chorionic villus sampling are invasive procedures during which cells are harvested from the amniotic fluid or the placenta. This is associated with a small risk (0.3 to 0.5 percent) of miscarriage. Some centres only look for the presence of trisomy 21, 13 and 18 (and any sex chromosome abnormalities) using these follow-up tests. Other centres also look for other microscopically visible chromosomal abnormalities, or employ new techniques (*chromosomal micro-arrays*) that also allow identification of sub-microscopic abnormalities.

FAS investigates all possible ultrasonographically observable structural abnormalities to the central nervous system, the spinal column, the face, the chest cavity, the heart, the abdomen and the limbs. However, FAS is also a care instrument that provides information (for example about fetal growth and the amount of amniotic fluid) that may be important for optimal care during pregnancy and delivery. Pregnant women often see this scan as a first opportunity to see their child. The uptake (about 90 percent) is much higher than for the combined test. If an abnormality is observed during this scan, it is not always clear what the clinical meaning is. The pregnant woman then qualifies for follow-up testing via advanced ultrasound examination, amniocentesis or both.

Normative framework for prenatal screening

Population screening is defined as: the offering of medical investigations to people who have no symptoms or other reasons to seek medical care for the conditions that are the target of the investigation. Screening is only justified if the usefulness of said offer has been proven, and the advantages for the participants clearly outweigh the disadvantages. For most forms of screening, this means that health gains may be achieved through timely treatment or prevention. This also applies to the prenatal screening programme for infectious diseases and blood group antibodies.

The situation is different for screening for fetal abnormalities such as Down's syndrome. The purpose is not health gain at all, but to inform a decision on whether or not to carry a pregnancy to term. If they carry to term, it allows those involved to prepare for the birth of a sick or handicapped child. If they do not, they avoid giving birth to a sick or handicapped child. No matter how difficult or painful, many pregnant women and couples feel it is important to be given the choice if the fetus does have a serious abnormality. Prevention as a social objective, focused, for example, on reducing care costs for people with congenital conditions or handicaps, is not the goal of such screening. If this were the case, those who claim that prenatal screening for fetal abnormalities is a discriminatory practice that sends the message that people with conditions and handicaps are unwelcome in society would be right. That the aim is entirely different – the provision of useful reproductive choices to the pregnant woman and her partner – must be demonstrated by the practice and offering of such screening tests.

The purpose of the Population Screening Act (WBO) is to protect individuals against high-risk forms of population screening, which includes psychosocial risks. The WBO requires permits for specific categories of population screening. One such category is screening for severe conditions for which no treatment or prevention options exist. Prenatal screening for fetal conditions was also (even specifically) considered during preparation of this bill. The Minister of Health, Welfare and Sports decides on permit applications after obtaining advice from the Health Council. When evaluating the application, the Health Council examines the scientific validity of the planned screening, whether it is in accordance with legal rules and regulations for medical actions and whether the risk-benefit balance is beneficial for the participants. A permit was issued in 2007 for the current screening for Down's syndrome and trisomy 13 and 18, as well as for FAS as a screening test for neural tube defects.

Development of non-invasive diagnosis and screening

Since the 1990s, there have been high hopes for what is now referred to as non-invasive prenatal test (NIPT). Non-invasive means that investigations into potential chromosomal abnormalities or genetic defects in the fetus are no longer necessarily associated with a risk of miscarriage or other complications related to amniocentesis or chorionic villus sampling.

The discovery of fragments of cell-free fetal DNA in maternal plasma in the late 1990s was a major breakthrough. Cell-free fetal DNA-based tests have since been developed that can be used for diagnosis and screening, referred to as NIPT. Current applications include sex determination within the context of prenatal diagnosis, for example if the pregnant woman is a carrier of a sex-linked disease such as haemophilia or Duchene's muscular dystrophy, or for the prevention of unnecessary treatment of a male fetus in pregnant women at risk of having a child with androgenital syndrome (AGS). NIPT is currently also used for non-invasive diagnosis of autosomal dominant conditions in which the male partner (and not the pregnant woman) carries the mutation responsible for the disease. The first application of NIPT within the context of prenatal screening is testing fetRhesus D status in fetuses of RhD negative pregnant women. NIPT as a test for chromosomal abnormalities such as Down's syndrome and trisomy 13 or 18 is based on *massive parallel sequencing* (MPS) of cell-free DNA fragments. MPS can show, for example, that maternal plasma contains more DNA molecules from chromosome 21 than would be expected if the pregnant woman and the fetus both had a normal chromosome pattern.

A recent systematic review found that NIPT for trisomy 21 does not allow final diagnosis. As a screening test it might well have better properties than the current combined test. Based on recent studies, test sensitivity is 99.5 percent and specificity is 99.7 percent. This means that 0.5 percent of trisomy 21 cases is not identified (false negative) and that in 0.3 percent of pregnancies without trisomy 21, a positive test result is given (false positive). However, as most studies are focused on the performance of the new test in high-risk pregnancies, it remains insufficiently clear to what extent these positive properties also apply to the general population, where the prevalence of trisomy 21 is lower. Therefore, the new test is not yet recommended as an alternative to the combined test within the context of screening programmes, neither in the Netherlands or abroad. NIPT is offered to pregnant women with an elevated risk due to a positive combined test as second (follow-up) screening test. The advantage of this over the current approach to screening is that pregnant women almost always receive a reassuring

(negative) test result in such cases, which is also highly reliable. An invasive test would only follow in the event of an unfavourable (positive) NIPT result, because a final diagnosis is needed if the pregnant woman is to consider terminating the pregnancy. This strategy with NIPT as second screening test can significantly reduce the number of invasive procedures. A disadvantage of NIPT is, that it sometimes fails and needs to be repeated (or an invasive test has to be performed instead).

Once the validity of NIPT as a test for Down's syndrome (and trisomy 13, 18) can be sufficiently established in the general population, the question whether NIPT should be used as first-line screening test – instead of the combined test – may arise.

Ethical aspects of prenatal screening with NIPT

The greater sensitivity of NIPT as first line screening means that compared with the combined test, more pregnancies with the targeted chromosomal abnormality will be identified. This is important, because more participating pregnant women will then receive reliable information that provides them with a reproductive choice that they would otherwise not have had. Other advantages are a significant decrease in the number of pregnant women who are needlessly exposed to uncertainty, fewer invasive procedures and fewer miscarriages and other complications due to such procedures. The importance of a test that is better on all aspects is underlined by a recent study of beliefs among pregnant women, which showed that the uncertainty associated with the combined test is a key reason not to participate in the current screening programme.

The potential disadvantages of NIPT can be summarized as routinization. The disadvantage of a simple, safe test may be that participation is considered self-evident and presented as such by care providers. This may lead to pregnant women (and their partners) not fully realising that the test results may leave them with a major and possibly extremely difficult decision. Worries about routinization as the downside to the potential advantages of NIPT is primarily associated with the at least at present unrealistic scenario in which NIPT would allow final diagnosis (one-step scenario). However the Committee is of the opinion that also the scenario in which NIPT as a first-line screening test replacing the current combined test harbours a risk of routinization. Ironically, the introduction of a test that may bring useful reproductive choices to more pregnant women may undermine said goal in practice, as pregnant women may feel pressured to submit to such screening.

The Committee believes the fact NIPT can provide information on the sex of the fetus at an early stage during pregnancy is worrying, as this information may be used by some pregnant women or couples to decide to abort due to undesired sex. It should be noted that NIPT is not only becoming available via health care (prenatal screening or diagnosis), but is also being offered commercially, among other things for sex determination.

Future developments: broadening scope, blending of goals

To date, technical limitations and cost have dictated screening options rather than criteria based on content. However, once NIPT can be deployed with a narrow or genome-wide spectrum, the question of the desired scope of screening will become unavoidable. A key condition is that advantages for participants must outweigh the disadvantages (proportionality). In the opinion of the Committee, it remains to be seen whether this is the case for genome-wide prenatal screening. Potential disadvantages include the risk of unclear outcomes, identification of risk factors for a late-onset disease, and finding abnormalities and risk factors related to a phenotype that is expected to be mild. The difficulty with such outcomes is that the pregnant woman (and her partner) may be presented with difficult to handle and burdensome choices. Another key question is whether informed choice is feasible for genome-wide prenatal tests. If the choices in question are not actually made by the pregnant woman and her partner, they will unavoidably be determined by the desires and interests of others. This includes the technological imperative, the research agenda of some professionals and, via an indirect route, the interests of society in preventing the birth of children with expensive conditions or handicaps (prenatal screening as prevention).

A separate but important question is how to take the interests of the future child into account when performing genome-wide NIPT. If it becomes possible to sequence and analyse the entire fetal genome in maternal plasma in the future, how can it be prevented that acquiring said information will rob the unborn child of his ‘right to an open future’? NIPT is expected not only to result in a broader scope for screening for fetal abnormalities, but the distinction between diagnosis and prenatal screening for conditions relevant to good pregnancy outcomes will become blurred if NIPT would increasingly be used for the latter as well. This includes mapping gene expression patterns that predict pregnancy complications and fetal developmental disorders, for example, as well as findings that can lead to medical treatment for the fetus. This creates a confluence of various prenatal screening goals (health gains and treatment options), which is already an issue

present with FAS. As with FAS, there is a risk that self-evidence of one goal can cause that sight of the aspect of choice implied by the other is lost. To prevent this, the Committee believes the options intended for specific purposes must be presented separately wherever possible.

Conclusions and recommendations

NIPT as an early, completely safe and direct diagnostic test is not currently a feasible option. A realistic scenario is NIPT as the first follow-up test after a combined test indicating an elevated risk of trisomy. In time, NIPT may prove an alternative to the combined test. Although screening with NIPT can currently be considered, at most, safer and more reliable than the current approach, the Committee believes this suffices for consideration of NIPT in the screening programme. It particularly means that disadvantages of the screening for participants decrease, increasing the appeal of the advantages of participation (the intended reproductive choice) for a larger group. Removing impediments can lead to improved achievement of screening goals. The Committee does feel that implementation studies should explicitly examine the potential disadvantages, such as the fact NIPT sometimes fails.

To date, the worries discussed in the literature on NIPT are primarily concerned with the possibility of routinization as a downside to an improved screening procedure. This may come at the cost of careful decision making, and make screening options vulnerable to the criticism that what is labelled reproductive autonomy is in fact nothing more than preventing the birth of children with conditions and handicaps that are costly for society. The Committee does not consider this a valid reason to reject improvement of current screening processes with NIPT. However, it does mean the development of daily practice must be carefully examined within the context of screening objectives. And that providing careful information and counselling will be no less important as screening tests become simpler, more reliable and safer.

There are currently differences between centres in terms of approaches to follow-up testing, and the issue of which test results are shared with the pregnant woman. These differences result in treatment inequality for participants in the national screening programme, and raise the question of what follow-up testing should be considered appropriate. The Committee believes consensus on this topic is desirable.

An unavoidable question for the future is what the scope of screening tests should ultimately be, who should make the decisions, and based on what criteria. The Committee notes that assuming the goal of 'providing meaningful reproductive choices' is best served by screening that is as broad as possible, is too simplistic.

The Committee expects that the developments outlined in this monitoring report will have a major impact on the daily practice of prenatal screening in the coming decade. There is a strong need for steering focused on a responsible and timely transition to *prenatal personalised medicine*. How future-proof the current normative framework is, as well as the role of the WBO in this area, must also be examined critically.