Summary of a report - Analysis of fetal DNA in the woman's blood: Non-invasive prenatal testing (NIPT) for trisomy 13, 18 and 21 – ethical aspects

This text summarises The Swedish Council on Medical Ethics discussion and positions taken in the report *Analysis of fetal DNA in the woman's blood: Non-invasive prenatal testing for trisomy 13, 18 and 21 – ethical aspects* that was published in October 2015.

Introduction

NIPT (Non-Invasive Prenatal Testing) offers ethical and medical advantages over currently used prenatal diagnostic methods. The test can be performed earlier in pregnancy, is simple and free of risk and provides a reliable result. Amniocentesis can be avoided, meaning fewer miscarriages and less inconvenience for the woman. Simplicity and reliability may, however, be disadvantageous from the ethical point of view.

Prenatal testing leads to ethical considerations that include value conflicts and conflicts of interest. In particular, issues arise over the significance of prenatal testing in the way human dignity is viewed and whether it is respected. The fundamental ethical problem with prenatal testing is the conflict between the interest of the parents in obtaining information about the fetus, on the one hand, and the requirement of respect for human dignity and concern over the societal consequences that use of the technique might create in the longer term, on the other.

Value-based ethical perspectives can also be based on how and to whom prenatal testing should be offered. Prenatal testing and NIPT thus also raise issues of fairness and priority.

Those concerned

Those concerned primarily include the pregnant woman, the fetus, the pregnant woman's partner and the siblings of the expected child. Others are individuals who carry a chromosomal abnormality and their families. Important stakeholders also include healthcare professionals, those responsible for antenatal care, the medical units taking samples, the genetic laboratories performing the NIPT analysis and decision-makers in county councils.

Arguments that can be cited in favour of NIPT

- The test is non-invasive and therefore does not pose any risk of miscarriage.[1]
- Using NIPT avoids the mental or physical inconvenience that may be caused by the invasive methods used at present (amniocentesis and chorionic villus sampling).[2]
- After NIPT, the woman receives a very reliable result. False-negative tests are rare. The number of false positives is substantially lower than with combined ultrasound and biochemical screening (CUB).
- The test being reliable and free of risk gives the midwife/genetic counsellor/doctor more time (than in the case of information prior to CUB and amniocentesis, for example) to focus on information about what a possible test entails and can provide in the way of results, as well as any consequences and choices the woman may face.

[1] An invasive test is, however, currently recommended if the test result is positive, to verify the result, in view of the proportion of false-positive results.
[2] Invasive testing is, however, currently recommended to verify a positive test result.

- The method will be more cost-effective in the long term than the methods of probability assessment and genetic prenatal testing used at present.
- A larger proportion of women carrying a child with the chromosomal abnormalities 13, 18 and 21 will be identified.
- Earlier monitoring makes any prenatal medical interventions possible and gives the woman and her family more time to assimilate the diagnosis and receive support prior to the delivery.
- The fact that testing can be performed early in the pregnancy puts the woman in a better position to make a well reasoned decision in the event of a trisomy diagnosis.
- The worthiness of protection of the fetus, according to the Council's previous positions, is weaker during early pregnancy.

Arguments that can be cited against NIPT

- If the testing is regarded as routine, there is a risk of it being done without reflection, and without fully understanding what the results might show and what information it may be necessary to deal with.
- It is difficult for the pregnant woman to turn down a harmless test, which may mean that her options are indirectly restricted.
- There is a danger of pregnant women who decide against risk-free genetic prenatal testing being called into question.
- More fetuses with chromosomal changes being discovered early in pregnancy will probably lead to more abortions of such fetuses.
- The combined effects of a new, more effective prenatal testing method may be that fewer children with chromosomal changes are born. This may mean that the way we view human dignity is radically altered, and there is

also a risk of us contributing to the acceptance of human diversity being increasingly restricted. It is pointed out by the disabled movement, among others, that prenatal testing as such is discriminatory and that there is a risk of it leading to greater stigmatisation of people with disabilities in society.

Discussion, considerations and positions

Human dignity and equal treatment

The Council takes as its starting point the view that the coming into being of human life is a process, where the fertilised egg is a life in the making with a certain worthiness of protection. This worthiness of protection increases gradually during the course of development. At the time when the fetus may be viable outside the mother's body, the worthiness of protection of the fetus becomes a matter of human dignity.

To enable prenatal testing in healthcare to be applied in an ethically acceptable way, it is important that the objective of this activity and the actual offering of prenatal testing are formulated in such a way that they cannot appear to single people out or be discriminatory or stigmatising, for example with regard to Down's syndrome. Another condition to be met is that the offering of and information on prenatal testing must be non-directive; instead, it must be something that the woman herself has to decide upon.

More fetuses with chromosomal changes being detected early in pregnancy may lead to more abortions of fetuses carrying such abnormalities. The idea that an early abortion is less medically risky and less problematic from an ethical point of view may possibly lead to increased pressure on the woman from those around her to abort a fetus with chromosomal changes.

The combined effects of a new, more reliable prenatal testing method may mean that few children with chromosomal changes will be born. It is therefore of particularly great significance that there is good societal support for people with disabilities. A continuous debate in society on the equal value of people is

important. The Council's discussions have also touched on the fact that differences among individuals in a population may have positive effects from a development perspective.

Informed choices

If the new method is offered to all pregnant women, it is possible that it will come to be regarded as a routine examination, i.e. a form of screening. It is therefore important to evaluate and safeguard how information is to be provided and how the offering is to be formulated prior to introduction of NIPT as a first-line procedure. The quality of information on prenatal testing should be reviewed in a similar way to the review of biomedical methods.

If it is to be ethically acceptable to introduce NIPT in the health service, it must be ensured that the information and the offering are formulated in a way that ensures that the pregnant woman and her partner can make an independent decision. It must be evident from the information given at the time of testing that NIPT is not a routine procedure but an opportunity for the woman to receive more information about the fetus. The woman therefore has to decide for herself whether or not she wants this.

The information should clarify what may be discovered through the test, the limitations of the test and describe what a diagnosis of trisomy may mean for the future child. It is also crucial to ensure through discussion that the woman receives the information she wants and that she has understood the contents of the information in accordance with current regulations.

If NIPT shows a high probability of chromosomal change, the information should not only contain the possibility of abortion. It is just as important that the woman and her partner are informed about what support society can offer.

It is also crucial to examine what impact the regulations and general guidelines of the National Board of Health and Welfare on prenatal testing have had, focusing in particular on how the offer of prenatal testing is formulated and how information is provided. If they are not followed, it is important to find out why, and create what is needed to deal with this.

The slippery slope

A method being permitted may signify both an 'indication drift' and an 'acceptance drift'. If a new method of treatment or diagnosis is effective, the area of use tends to be broadened. The method may come to be used to diagnose more diseases or characteristics. This is known as an indication drift. NIPT is a method with great development potential, and a method with an area of use that will in all probability be rapidly expanded.

The Council has further discussed the importance of ethical and medical re-assessment before the same technique is used for other predispositions or conditions. In this context, there is a real possibility of whole-genome sequencing and of the parents demanding full information on the DNA of the future child, which raises several difficult ethical issues, in particular concerning the genetic privacy of the future child.[3]

The second part of the slippery-slope argument is concerned with whether this technique opens up an acceptance drift that, in the long term, means that the values of society regarding the possibility of finding out in a simple way more and more about the genetic make-up of the future child are shifted. Can this lead to more extensive weeding-out of fetuses, based on an ever lengthening list of what are regarded as "undesirable" characteristics and conditions? This issue is linked to how our view of humanity may change in the future.

Introducing NIPT for the analysis of trisomy 13, 18 and 21 in the health service must not lead to the test being offered for more abnormalities and pathological conditions without medical and ethical re-assessment at national level.

[3] For a discussion of risks associated with further use of NIPT by expectant parents, see for example Deans et al. 2015 and Hermerén 2015.

Fairness aspects

Equality of care

There are differences in the use of prenatal testing related to socioeconomic status and origin.[4] It is crucial to find out why these differences exist and tackle the shortcomings that may be due to inequality. There is a risk of socioeconomic status, educational background, linguistic proficiency or cultural background dictating what testing the individual is offered, in which case the care provided becomes unequal.

There are also wide regional differences today with regard to the offer of prenatal testing. Where an individual pregnant woman lives should not determine whether or not she will have access to the method regarded as best. At present there is scope to seek care in different county council areas and thus a possibility of choosing a method that the individual woman's home county council does not offer. However, this presupposes first that the individual woman knows where a desired test is offered and secondly that she has the financial capacity to travel and if appropriate take time off work without pay or lose unemployment benefit. There is currently also provision for paying for NIPT oneself. Both these situations highlight the issue of equality of care. A discussion of joint strategies in the introduction of NIPT in the healthcare system would be desirable, possibly under the umbrella of the Swedish Association of Local Authorities and Regions.

The new method can either be introduced at the same time throughout the country or gradually by trying out the method first in one county council or a few county councils and then introducing it nationwide. If the principal aim is to achieve equality of care, the method should be introduced almost simultaneously throughout the country. A drawback with uniformity of this kind is, however, that implementation may take a considerable time and that each new method in a sense becomes a full-scale experiment. If instead new methods are tried out in a single county council, it is possible to gain valuable experience that can guide others. The

[4] See p. 16.

drawback with such a step-by-step introduction is that women's access to the method will vary with place of residence during a transitional period.

Who should the method be offered to?

The question "Who is the method to be offered to?" raises a whole range of ethical issues. There are a number of options, all of which entail advantages and drawbacks:[5]

- All women are offered the test.
  Justification: fairness and equality.
  Dilemma: screening/stigma/eugenics/costs
- All women who ask for the test are offered it.
  Justification: fairness, equality, respect for the right of the pregnant women to be informed/respect for informed choice.
  Dilemma: socioeconomically weak groups may be disadvantaged.
- All women who may benefit from the test are offered the test.
  Justification: needs/benefits, cost-effectiveness.
  Dilemma: difficult to decide which women may benefit from the test.
- All women who have an increased probability of carrying a child with chromosomal abnormalities are offered the test.
  Justification: needs, cost-effectiveness.
  Dilemma: difficult to decide which women these are. A test that is offered to a group of women with a higher probability of having a baby with trisomy 21, for example, may appear to single individuals out and lead to stigmatisation and discrimination.

[5] The examples are taken partly from Hermerén 2015. Others who have analysed the problems associated with various ethical aspects of different models for introduction into the healthcare system are Deans and Newson 2012.

Specific aspects of age as a method of selection

As NIPT does not pose a risk of miscarriage or discomfort for the woman, the "risk argument"[6] no longer persists to limit the offering of genetic prenatal testing to women who have an increased probability of chromosomal changes in their fetus. If the new method is to fulfil the requirement of care on equal terms, the method should be offered to all pregnant women.

In several parts of Sweden, however, only women over the age of 33–35 are offered extended/genetic prenatal testing. An offering to this group of women has been justified by women over the age of 35 statistically having a higher probability of giving birth to a baby with a chromosomal abnormality. Individual probability assessment with a combination of ultrasound scanning and biochemical testing has, however, to date been a better method of selection than age as regards which women are to undergo genetic prenatal testing. Age is not a good method of selection in deciding who should be offered NIPT.

An offering of NIPT aimed solely at a group of women who are estimated on the basis of age as having an increased probability of carrying a child with trisomy 21 may in itself appear to single out and be discriminatory for individuals who have trisomy 21. It may also indirectly indicate a different aim of prenatal testing than the woman having the possibility of receiving information about the fetus she is carrying. An offering targeted solely at a specific group of women may also be perceived as being more directive. It is crucial to exercise caution in how prenatal testing is offered by the healthcare provider and how information is given.

Genetic prenatal testing as screening?

An offering of NIPT to all pregnant women may entail a form of screening. Such action may be perceived as showing that society wishes to influence the pregnant woman to have prenatal testing,

[6] Invasive testing is associated with risk of miscarriage. Based on a risk/benefit analysis, it is not justifiable to offer this testing to women who do not have a statistically higher probability of carrying a fetus with chromosomal abnormality or other genetic disease. This argument does not apply to NIPT.

and indicating that it is not a case of an offering to the pregnant woman upon which she herself has to decide.

The WHO criteria for screening in the neonatal period may also be important for screening in prenatal testing. These criteria include requirements that it must be possible for a detected disease to be treated. Genetic screening programmes for prenatal testing can be justified only if there is an effective treatment for the hereditary disease concerned.

To enable NIPT to fulfil requirements for equality of care and to reduce the probability of it being regarded as screening, the information on prenatal testing should be provided in two steps. NIPT must be offered only if it can be ensured that the woman has had an opportunity to make an informed choice. It should be clearly apparent from the information given ahead of NIPT what can be detected by the test and what the consequences are for the health of the future child. It must be clear that it is an *offer* that can be declined.

Priorities, health economics and ethical values

We can differentiate between NIPT as a test that is offered as a second step or as a first step.[7] Two questions should guide a comparison of strategies:

(a) What – and whose – values are at stake? Who wins and who loses what?
(b) What do the various alternatives cost? What is the cost in relation to the effect? Identify what aspects need to be included in the setting of priorities.

Strategy 1. NPT as a second-step test, i.e. if the probability > 1 in 200 based on CUB.

A variant would be to offer NIPT as a second step after probability assessment based on CUB to reduce the number of invasive tests.

[7] NIPT as a first- or second-line test is also discussed in the international literature, see for example Dondrop et al. 2015, etc.

As NIPT today costs more than CUB but less than an invasive test, the assessment could be made on the basis of a cost-effect argument that the offering of NIPT should be limited, for example by only offering the test to women who according to CUB have an increased likelihood of a fetus with a chromosomal abnormality.

Advantages:

- Can easily be introduced in the current organisation for prenatal testing (in those county councils where CUB is already offered).
- Fewer invasive tests than in the present-day procedure.
- Prenatal testing being done in several steps may increase the scope for the woman to reflect on whether she wants to undergo genetic prenatal testing.
- Can probably be introduced without additional costs.

Drawbacks:

- Only around 90% of chromosomal abnormalities are detected; several women receive a false-negative result.
- More women receive a false-positive result, which may have adverse consequences for the woman in the form of anxiety and even dissociation with the ongoing pregnancy.[8]
- Women miss out on the advantage of receiving a definitive result earlier on in pregnancy (which they would have received if they had been offered NIPT in a first step).
- A complicated procedure regarding information on the offer of prenatal testing. It may be difficult to justify why everyone cannot be given access to the more reliable test immediately.

Strategy 2. NIPT as a second step but with a more generous offering. CUB → NIPT if the assessment of probability is 1:51–1:1000 → invasive procedure if increased probability based on NIPT. CUB → immediate invasive procedure if the estimate of probability is >1 in 50.

[8] Several studies point to adverse consequences for pregnant women who are given a false-positive result according to NT/CUB (nuchal translucency scan/combined ultrasound scan and biochemical testing) if the child has an increased probability of chromosomal abnormality. See for example Georgsson Öman et al. 2006.

This strategy is based on NIPT being offered in a second step instead of invasive testing and being preceded by an ultrasound scan as part of CUB to investigate whether the woman should be offered extended genetic prenatal testing. In the case of a CUB probability of 1 in 50, invasive prenatal testing is offered with complete karyotype or microarray. The majority of trisomies and chromosomal abnormalities of clinical significance not detected by the NIPT test today are in this group.

This strategy is under discussion by the profession in Sweden and will probably be supported by SFOG (Swedish Society of Obstetrics and Gynaecology) in its forthcoming recommendations on the introduction of NIPT.

Advantages:

- Can easily be introduced in the current organisation for prenatal testing (in those county councils where CUB is already offered).
- Fewer invasive tests compared with the present-day procedure (but probably more invasive tests than with strategy 1 above).
- Prenatal testing being done in several steps may increase the scope for the woman to reflect on whether she wants to undergo genetic prenatal testing.
- More rare chromosomal abnormalities can probably be detected than with the present-day strategy and the strategy above and if NIPT is offered in a first step.

Drawbacks:

- Fewer of the most common chromosomal abnormalities are detected than if NIPT were to be offered in a first step. More women receive a false-negative result.
- More women receive a false-positive result, which may have adverse consequences for the woman in the form of anxiety and even dissociation with the ongoing pregnancy.[9]

[9] Several studies point to adverse consequences for pregnant women who are given a false-positive result according to NT/CUB (nuchal translucency scan/combined ultrasound scan and biochemical testing) if the child has an increased probability of chromosomal abnormality. See for example Georgsson Öman et al. 2006.

- Women miss out on the advantage of receiving a definitive result earlier on in pregnancy (which they would have received if they had been offered NIPT in a first step).
- A complicated procedure regarding information on a complex offering of prenatal testing.
- Costs more than the present-day strategy and strategy 1.

Strategy 3. NIPT as a first step. NIPT → invasive procedure if increased probability based on NIPT

Advantages:

- More chromosomal abnormalities will be detected.
- Almost no false-negative results. Almost no women will be lulled into a false sense of security.
- Fewer women will receive a false-positive result.
- More women can be given a definitive result earlier in pregnancy (the test can be performed in weeks 9–10 of pregnancy), which gives her and her partner more time to think about what a positive test result might mean.
- It may be easier for antenatal care to inform the woman what the test is, and it may be easier for the woman to understand what the test entails and what issues she may face.

Drawbacks:

- If the test is regarded as routine, there is a risk of women undergoing the test without reflection, and without fully understanding what the results might show and what consequences it might have.
- If the test is done in weeks 9–10 of pregnancy, it is possible that chromosomal abnormalities will be detected that would in any case have led to a spontaneous abortion.
- Searching only for trisomy 13, 18 and 21 may lead to other abnormalities and malformations being missed.
- Virtually all chromosomal abnormalities of 13, 18 and 21 will be found; this may be regarded as negative if positive results always lead to abortion.
- An expensive strategy at present.

Strategy 4. NIPT as a first step but complemented by an extra early ultrasound.

Ultrasound + NIPT → invasive procedure if there is an increased probability based on NIPT, invasive testing immediately if malformation of the fetus is present on the ultrasound.

The same argument as above, with the difference that uncommon abnormalities and conditions can probably be identified earlier in the pregnancy through an extra early ultrasound. This strategy would, however, be expensive.

The Council's discussion and positions

From an ethical perspective, NIPT as a method is preferable to both CUB and invasive testing. The test should therefore be introduced in the longer term as a first-line test, given that the costs are reasonable in relation to effectiveness and other needs in the healthcare system.

The Council finds, however, that it may be ethically acceptable to introduce NIPT as a second-line test on introduction of the method in the healthcare system. At present it is organisational and cost arguments in particular that favour the test being introduced as a second step (after CUB) in prenatal testing. However, the Council sees advantages in introducing the test step by step in the healthcare system, and introduction in a second step may therefore be justified above all on the basis of arguments on quality assurance and to limit costs. This procedure makes it possible to assure the quality of methods of providing information on NIPT to ensure that an informed choice can be made by the pregnant woman or couple. This strategy provides scope to introduce the method in an orderly manner.

Introducing NIPT as a first-line prenatal test in the longer term requires reorganisation of the prenatal testing part of antenatal care, and adjustment of the way in which information about prenatal testing is given and the offering is formulated. Safeguarding the woman's informed choice is a fundamental requirement which must be met if the activity is to be ethically

acceptable. Genetic prenatal testing as screening is not desirable, as explained earlier.

Various aspects of offering CUB before NIPT

The health service first performing a hormone test and then later a genetic test with considerably higher reliability may be justified on grounds of cost. From a patient perspective, however, this arrangement may appear difficult to understand, and it may lead to worry. This arrangement may also lead to unfairness and inequality. Certain socioeconomic groups may be disadvantaged. Women with the necessary knowledge and financial resources may, for example, if they are not offered NIPT, pay for their own testing or directly ask for NIPT rather than CUB.

Future development

The advocates of molecular genetic mapping believe that we will take the step from reactive medicine to proactive medicine. It is important in this context to remember that the aim of prenatal testing is not to refine and improve but, through an early selection, to do good, and avoid lifelong suffering and severe disability. The final outcome of the two methods of selection may, however, be very similar.

The Swedish National Council on Medical Ethics (SMER) has on repeated occasions cited the need for detailed information and genetic counselling in connection with genetic testing, whether performed in or outside the health service. Training efforts aimed at antenatal care are needed in connection with the introduction of NIPT. There is also a need for genetic counsellors.

Developments in the area of prenatal testing may also have an impact on the insurance system. Who is willing to insure someone who we know with a very high level of probability will have a serious illness? What do we do with future generations? The willingness of insurance companies to accept risk is, and has to be, limited.

The new-generation prenatal tests such as NIPT raise issues regarding clear demarcation of what form of offering of prenatal

testing should be provided under publicly funded healthcare. What is to be sought out and why?[10] Should the possibility of parents seeking out genetic information about their fetuses and children which is not medically justified be limited?

[10] For a discussion on future prenatal testing based on expanded options due to NIPT, see for example Göran Hermerén, 2015 and Christian Munthe, 2015.