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## **Implementing Non-Invasive Prenatal Testing (NIPT): Perspectives of patients and professionals**

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# **CHAPTER 1.**

## **GENERAL INTRODUCTION**



## **PRENATAL SCREENING**

Prenatal care is a dynamic and continuously evolving field. Over the years many new technologies have been introduced to promote optimal health of the mother and child. During pregnancy, women are offered various medical check-ups and screening tests to assess blood pressure, possible infectious diseases, blood group, rhesus factor and other potential risk factors.(1) Pregnant women are also offered prenatal screening to determine whether the fetus has a congenital disorder. This provides prospective parents with information about the health of the fetus and allows them to make an (informed) reproductive choice. The implementation of new, advanced technologies in prenatal care requires careful consideration and close collaboration between all involved stakeholders.

### ***Prenatal screening for fetal aneuploidy in the Netherlands***

In the Netherlands, prenatal screening for fetal aneuploidy has been available for several decades. Today, the risk of three fetal trisomies can be assessed: Down syndrome (trisomy 21), Edwards syndrome (trisomy 18) and Patau syndrome (trisomy 13). Down syndrome (DS) is the most common chromosomal abnormality and occurs in the Netherlands in around 1 in 500 pregnancies.(2) The prevalence of trisomy 18 and 13 is lower and these disorders are associated with poor life expectancy.

Prior to 2007, Dutch women were offered prenatal screening based on maternal age alone because of an increased risk of DS with advanced maternal age. Women of 36 years or older were offered invasive testing, either by chorionic villus sampling (CVS) or amniocentesis. These procedures are highly accurate and can be performed between 11 to 14 weeks of gestation (CVS) and from 16 weeks gestation onward (amniocentesis). The disadvantage of these procedures is the associated miscarriage risk of 1:200 and 1:300, respectively.(3) To limit the number of women exposed to this risk, while enabling reproductive choice, a nationwide screening program using the first-trimester combined test (FCT) was introduced in the Netherlands in January 2007. The FCT can be performed between 11-14 weeks gestation and consists of an ultrasound examination to measure nuchal translucency, and a blood test to measure maternal serum markers (PAPP-A and free betaHCG). Combined with maternal age, these measures generate an individualized risk for trisomy 21, 18 and 13.(4) Women with a risk of 1:200 or greater are considered to be at increased risk for fetal aneuploidy and are referred for confirmatory invasive testing at a Prenatal Diagnostic Center (or can decide to have no further testing). Although the FCT is safe, it does have a false-positive rate of around 5-7%,(5;6) meaning that 1 in 20 women are identified to be at increased risk while not actually carrying an affected child. This causes many women to be unnecessarily referred for a risky invasive test. Moreover, about 1 in 5-10 cases of Down syndrome are not identified by the FCT since the sensitivity lies between 80 to 90%.(5;7)

Although one of the aims of offering the FCT to the whole pregnant population was to reduce risky invasive testing, the implementation of this test was preceded by numerous political and social discussions.(8) The idea of prenatal screening for all pregnant women raised concerns regarding social pressure to screen and 'collective eugenics'.(8) To avoid 'normalization' of prenatal testing, and since the FCT performed better in women of  $\geq 36$  years, the FCT (~150 euro) was only reimbursed for this group. Moreover, before offering the test, it became a prerequisite for the health professional to ask women whether they wish to be informed about screening or not. Since 2015, direct access to invasive testing for women of  $\geq 36$  has been abandoned and age is no longer considered an indication for reimbursement of FCT. Costs are only reimbursed for women with a medical history, such as an earlier child with an aneuploidy.

Compared to the uptake of prenatal screening in other European countries like England (74%)(9) or France and Denmark (>90%),(10;11) the Netherlands has a relatively low uptake of approximately 27%.(12) The proportion of DS pregnancies that end in a termination of pregnancy after prenatal diagnosis varied in European regions over the period 1990-2009 from 73% in France to around 50% in Denmark and UK to 0% in Poland and Malta.(13) Of Dutch women who choose to have screening and receive a high-risk assessment after FCT (5-7%),(12;14) around half choose confirmatory invasive testing.(14;15) When Down syndrome is confirmed with an invasive test, around 74% of Dutch women choose to terminate the pregnancy, although higher percentages were reported in earlier years.(16)

### ***Legislation and monitoring***

In the Netherlands, prenatal screening for congenital disorders is regulated by the Dutch Population Screening Act established in 1996 to protect people against potentially harmful screening. According to the act, the Minister of Welfare, Health and Sports (VWS) needs to issue a license -advised by the Health Council's Committee on Population Screening- before allowing organized population screening for cancer, for screening involving the use of ionizing radiation, or to screen for disorders with 'no available treatment' or prevention. The latter includes prenatal screening for Down syndrome.(8) Implementing a new prenatal test in Dutch prenatal care thus requires ministerial approval in the form of a license.

The Dutch National Institute for Public Health and the Environment/Centre for Population Screening (RIVM/CvB) coordinates and monitors prenatal screening and develops standardized information.(17) The execution of prenatal screening is realized through a chain of cooperating professionals such as midwives, sonographers, obstetricians, prenatal screening centers, and laboratories.(17)

## **NON-INVASIVE PRENATAL TESTING (NIPT)**

In 1997, the research group of Dennis Lo discovered that cell-free DNA (cfDNA) found in maternal plasma and serum can be used for prenatal diagnosis.(18) This knowledge was used to develop a non-invasive test for fetal sex determination and rhesus D testing.(19) Testing for fetal aneuploidies like Down syndrome proved to be more difficult. However, in combination with technological improvements in DNA sequence analysis (massively parallel sequencing, MPS) the non-invasive prenatal test for fetal trisomy became available in clinical practice in 2011.(20;21) With non-invasive prenatal testing using cfDNA, a simple blood draw of the mother is sufficient to test for fetal aneuploidy. Besides being a safe test, NIPT can be performed from as early as 10 weeks gestation onwards and has a sensitivity of more than 99% and a false-positive rate of less than 0.1%.(22) An abnormal NIPT result should always be confirmed by invasive testing (23-25) since discordant results caused by biological mechanisms like confined placental mosaicism, copy-number variations, mosaicism, and maternal chromosomal aberrations have been reported.(23) In public health based programs, NIPT or cfDNA testing can be used as a first- or second-tier test, (26) for which different scenarios have been described.(27)

- NIPT can be used as a second screening step for women who receive an elevated risk result for fetal aneuploidy based on conventional screening (FCT), as an alternative to invasive testing. NIPT is proven to have high sensitivity,(22) meaning that nearly all cases of trisomies 21, 13 and 18 can be identified among women at high risk after FCT. Due to the high specificity of NIPT, the majority of high-risk pregnant women will receive a normal NIPT result and thereby avoid having a risky invasive test. The introduction of NIPT as alternative for invasive testing will thus lead to a reduction in miscarriages and loss of (unaffected) fetuses.(28)
- NIPT can also be used as a first-tier screening test, replacing FCT. Studies show equally good test performance of NIPT in pregnant women with no a priori increased risk.(6;29) Although the positive predictive value of NIPT is lower in pregnant women with no increased risk than in high-risk pregnant women,(30) it still performs much better than standard screening (FCT) for chromosomal aneuploidies.(23) The sensitivity is much higher (>99% vs. 80-90%, respectively) and the false-positive rate of NIPT is only a fraction of that of the first-trimester combined test (FCT) (0.1% vs. 5-7%, respectively).(6;7;22) This means that fewer women would be unnecessarily referred for an invasive test and subjected to its miscarriage risk.(23)

### ***Widening the scope of prenatal screening with NIPT***

Technically, it is possible to scan the entire fetal genome using NIPT.(31;32) This finding, together with the rapid developments of NIPT suggest that NIPT will likely become available for the detection of many other treatable and non-treatable genetic disorders, ranging from congenital lethal disorders, serious non-lethal disorders with mental disability, to milder genetic conditions. Commercial providers of NIPT have already started to expand their offer to more conditions.(33) In the long run, it is expected that NIPT will also be used to detect fetomaternal risk factors (i.e. markers for preeclampsia or preterm birth), thus enabling adapted monitoring of a pregnancy.(34)

### ***Ethical considerations***

The superior aspects of NIPT have resulted in it becoming a popular test that is being rapidly introduced worldwide.(35) The advantages are clear: a test with high accuracy, which can be done from 10 weeks throughout pregnancy, causing invasive procedures to be indicated less often. Thus procedure-related miscarriages will become rarer and women desiring to be tested will receive a fast and accurate test result. However, concerns have been raised about the use of NIPT. The fact that NIPT is a safe test and requires only a blood sample could lead to 'normalization' of prenatal testing (trivial to offer and take), and put informed choice at stake.(36;37) The future prospective of using NIPT to test for more disorders raises the question of the future scope of prenatal screening(37;38) and evokes concerns about aborting fetuses affected with minor abnormalities or non-medical traits.(24;36;39)

### ***The importance of informed choice***

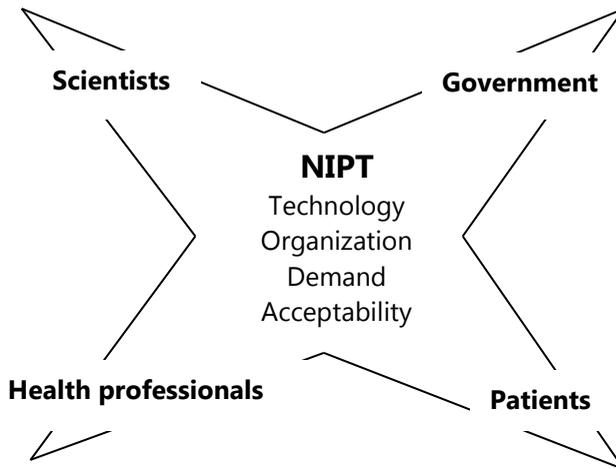
The aim of prenatal screening is to offer prospective parents the option of an informed and autonomous reproductive choice, rather than preventing the birth of children with a fetal abnormality.(24) This means that counseling and information provision should support prospective parents in making an informed choice about whether or not to have prenatal screening.(40) An informed choice is most commonly defined as a decision made with sufficient knowledge, consistent with the decision-maker's values and behaviorally implemented.(41) With NIPT, informed decision-making can be challenged. If the use of NIPT becomes routinized, or women feel pressured to have NIPT, this could potentially undermine informed decision-making and thus the aim of prenatal screening. If, in the future, NIPT were to be used to test for a wider range of disorders, informed decision-making could be further challenged by information overload and decisional complexity. With the implementation of NIPT it is thus essential to assure that prospective parents are still able to make an informed, autonomous choice.

## **NIPT IN THE NETHERLANDS**

From March 2011, the Dutch media started covering NIPT-related news. When the public became aware that NIPT was available abroad, increasingly, couples started traveling to Germany and Belgium to have NIPT performed in a clinic collaborating with commercial companies. A Dutch national NIPT Consortium was set up and meetings with the Ministry of Health, Health Council and Health insurers were organized to discuss offering NIPT in a nationwide evaluation research setting including all university medical centers. In March 2013, a license in accordance with the Population Screening Act was requested by the national Consortium for a trial on the implementation of NIPT (Trial by Dutch laboratories for Evaluation of Non-Invasive Prenatal Testing; TRIDENT study). In December of that year, the Health Council of the Netherlands advised to grant the license for the NIPT implementation study in high-risk pregnancies (women at increased risk after FCT ( $\geq 1:200$ )), followed by an approval from the Minister of Health for a (initially) two-year license. On April 1<sup>st</sup> 2014, the TRIDENT study started. In the TRIDENT study, women at high risk for fetal aneuploidy based on FCT results or based on medical history (e.g. previous child with a trisomy) are offered NIPT as an alternative for invasive testing.

### ***Stakeholders involved***

The implementation of a new technology like NIPT in Dutch prenatal care involves numerous people from different stakeholder groups (see figure 1). Obviously, prospective parents ('patients') play a central role as they are the end users of the test and create the demand. However, NIPT also causes changes in the daily practice of different health professionals and laboratory specialists, as they have to integrate NIPT in the current organization. Moreover, to evaluate the acceptability of NIPT in Dutch healthcare, regulatory and governmental agencies need to be involved and possible consequences for society (including people living with a disorder) should be taken into account.(24) In order to reach a sustainable implementation of NIPT, it is important to explore the attitudes of involved stakeholders and identify potential discrepancies between their views. For example, it has been shown that pregnant women consider the safety of a prenatal test to be important, while health professionals focus more on accuracy.(42) Pregnant women and health professionals also have different opinions on what the scope of a prenatal test should be.(43) Understanding these differences and taking them into account is an important part of the implementation process.



**Figure 1. Network of stakeholders involved in the implementation of NIPT in the Netherlands (based on:(44)).**

### **AIM AND RESEARCH QUESTIONS**

Since NIPT creates a significant change in prenatal care, the overall aim of this thesis is to get insight into the perspectives of the various stakeholder groups involved in the implementation process of NIPT. Exploring their views will stimulate the process of a responsible implementation of NIPT. Part I of this thesis explores the attitudes towards NIPT of pregnant women (and their partners), health professionals and parents of children with Down syndrome. Part II reflects on the implementation process of NIPT in the Netherlands and identifies the impact of NIPT on informed choice, emotional wellbeing, and satisfaction in high-risk pregnant women offered NIPT as an alternative to invasive testing within the TRIDENT study.

In this thesis the following research questions will be addressed:

Part I.

- 1. What are the attitudes of pregnant women (and their partners) towards NIPT?**
  - a. What are the potential implications of NIPT for fetal aneuploidy, and for screening for a wider range of disorders in the future, according to pregnant women? (Chapter 2 & Chapter 3)
  - b. For what type of disorders should NIPT be available in future and how should this be offered to pregnant women? (Chapter 3)
  - c. Why do pregnant women decline the FCT and how does this relate to future intentions for NIPT? (Chapter 4)
  
- 2. What are the opinions of health professionals on using NIPT for fetal aneuploidy, and for screening for a wider range of disorders in the future? For what type of disorders should this be available?** (Chapter 5)
  
- 3. What are the attitudes of parents of children with Down syndrome towards NIPT, and what implications do they think it will have?** (Chapter 6)

Part II.

- 4. What are the constraining and enabling factors for a responsible implementation of NIPT in the (Dutch) prenatal healthcare system?** (Chapter 7)
  
- 5. What are the experiences and decision-making process of high-risk women being offered NIPT as an alternative to invasive testing?**
  - a. Do high-risk women prefer NIPT or invasive testing and are they able to make an informed choice for NIPT? (Chapter 8)
  - b. How do women perceive the offer and procedure of NIPT and are they reassured by a normal NIPT result? (Chapter 9)

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