General discussion and future perspectives

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In 2007, a prenatal screenings program was introduced in the Netherlands. This program included the combined test (CT) which is on average performed at around 12-13 weeks of gestation, and the structural anomaly scan performed around 20 weeks of gestation. All women are offered the possibility to opt for prenatal screening. Once an increased risk (>1:200) or an increased nuchal translucency (>p99) is found during the combined test, or there is a suspicion on an anomaly during the structural anomaly scan, women are counseled on the possibility of prenatal diagnostics. One of the factors influencing women’s decision to opt for or decline chorionic villus sampling (CVS) or amniocentesis (AP) is the procedure related risk, which is lower than previously counseled 1%, in experienced hands.

LIMITATIONS

Limitations of Chapter 3, 7 and 8 are that measurements were performed on preselected images. As a consequence in Chapter 3 and 7 feasibility only relates to the success in obtaining measurements in the preselected images and not to the ability of obtaining the correct images, which might positively have influenced our results. In Chapter 8 this is also the case and during that study there was more time for postproduction measurements than normally in the clinic would be the case.

The importance of factors influencing image quality, e.g. gain and harmonics, are well known. From a technical point of view, the main contributor to intra- and inter-operator differences is the acquisition of the optimal image. This means that precision of measurements is still largely dependent on appropriate training, adherence to strict criteria, coincidental circumstances (e.g. fetal position, maternal BMI, time allocated) and, last but not least, on the operator’s personal attitude in terms of endurance and accuracy.

UPTAKE

In Chapter 2 we addressed the uptake of the CT and its determinants. The uptake of the CT since its introduction is around 30%, especially among women under the age of 36 years. This is considerable lower than the > 90% uptake of the 20 week anomaly scan. One of the criteria to evaluate the success of a national screenings program is its uptake. High uptake as success criterion is less obvious when it comes to prenatal screening: there is no effective treatment for the screened conditions that represent important health problems like trisomy 21, 18 and 13. Parents are offered choices that are supposed to increase their reproductive autonomy. Therefore it is important to allow women/parents to make an informed choice rather than to achieve an as high as possible uptake. Making an informed choice depends mainly on two things, the decision should be based on relevant information and it should be consistent with the decision makers’ values. So women should be aware of the option of prenatal screening, they should be adequately coun-
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selected, and when they take a decision it should be an informed one.

In Chapter 2 we also addressed the fact that the CT uptake is currently lower than uptake rates previously reported in research settings in the Netherlands (86% and 53% respectively). Like the Netherlands, a similar decreasing trend was seen in the UK, where uptake rates over the years decreased from 83% to 41% (1993-2005). Do women nowadays more often make informed choices? Shanta et al. concluded that attitude towards the CT and TOP had a larger impact on the uptake than knowledge on the CT. However, uptake rates in the UK are still higher than in the Netherlands, so cultural, societal or health system characteristics may also play a role. This brings us to the possible determinants of the low uptake of the CT in the Netherlands.

DETERMINANTS OF UPTAKE

Chapter 2 also addresses the determinants or reasons for women to decline the CT. These were mainly a positive attitude towards Down syndrome, a negative attitude towards termination of pregnancy, doubts about the reliability of the CT as screening test and fear for iatrogenic pregnancy loss when invasive diagnostics are indicated. Chapter 2 also gives the impression that Dutch women still perceive maternal age as a strong and reliable predictor of Down syndrome risk. Women of 36 years and older were almost five times more likely to opt for the CT than women below that threshold, and over one third of the younger women declined the CT because they considered their age-related risk to be low. According to literature, women’s perceptions of maternal age as strong indicator of Down syndrome risk and the inequality of access to care due to the financial threshold for younger women which existed until January 2015, has likely been influencing participation in screening. Both aspects, perceptions of maternal age and the perception of age-related copayment, will be discussed below.

DETERMINANTS: PERCEPTION OF MATERNAL AGE

The perception of women that their age is a strong predictor of Down syndrome risk can be understood from the prenatal screenings history of the Netherlands, which is unique in Europe. The 2003 advice of the Ministry of Health reads that the risk of trisomy 21 increased exponentially after a pregnant woman turned 36 years, justifying an invasive procedure. Although the age-related relationship may be justified from a descriptive point of view, the prognostic impact of maternal age in individual decisions is less obvious. It has long been known that maternal age as single risk factor is an inadequate prognostic model of screening for trisomy 21 (detection rate based on maternal age only: 30%) with the inherent risk of iatrogenic miscarriage, in comparison to the more comprehensive prognostic model of the CT (detection rate 90%). As a result, until 2015, advanced maternal age (≥ 36 years) was used as an accepted indication for direct invasive prenatal diagnostics in the Netherlands.

DETERMINANTS: COPAYMENT

Inequality of access to care was also present due to an age-related threshold for the reimbursement of the CT for women younger than 36 years (until 2015), discouraging them
to opt for this test.\textsuperscript{11} The 2003 advice of to the Ministry of Health (\textit{Kamerstukken}, 2003, 29 323, nr.1), mentioned two other relevant aspects. Firstly, that the CT would perform less well (in terms of predictive value) in younger women than in women of 36 years, and that it would lead to unnecessary medicalization of younger, supposedly low-risk, pregnant women, implying indirectly that this was an inferior test for this age group and therefore should not be recommended. However, later research has shown that the CT performs equally well in younger as in older women.\textsuperscript{14} It is likely that the age-related threshold, in combination with women's biased perception of their age-related risk influenced their risk perception and, consequently, their decision to participate in prenatal screening.\textsuperscript{11,12}

Recently, the Ministry of Health decided that the CT should be accessible to all women irrespective of their age from the 1st of January 2015. Since then however, all pregnant women in the Netherlands have to pay for the CT, while the structural anomaly scan is free of charge. Studies have shown that personal costs or co-payment may play a significant role in the decision whether or not to opt for the CT.\textsuperscript{12,15} Research among women accepting or declining the CT showed that co-payment in itself was not per se a reason to accept or decline, but women who declined the CT perceived it as extra confirmation that the test was not necessary whereas women accepting the CT thought it would discourage others from taking the test causing inequality of care.\textsuperscript{11} As a consequence, this financial threshold may now also discourage women of 36 years and older to opt for this test. Access to prenatal screening should be free of charge for all women so their decision is based on willing to know their individual risk for a trisomy in this pregnancy and not on whether or not they want to pay or are able to pay for this test. It seems that we have substituted the age-related threshold for a financial one.

**DETERMINANTS: COUNSELING**

Besides access to care, the quality of counselling is also likely to affect women's decision to opt for or decline prenatal screening. A study by Crombag et al. showed that women who intended to decline prenatal screening often referred to their low a priori risk of trisomy 21 according to the age-related risk tables in the information leaflet and perceived support for their decision to decline by their midwife.\textsuperscript{11} The national information leaflet states that 'The mother's age affects the likelihood of a child with Down syndrome', but does neither reveal if the mother's age is the single determinant, nor how large the impact on the likelihood of Down syndrome is. Alternatively, a clearer statement could be that maternal age is part of the risk assessment and not the only determinant of risk, as we already suggested in Chapter 2. To avoid over-emphasis on maternal age, the age-related risk table could be removed from the leaflet, since this table can be interpreted in different ways (e.g., comparing age-related risks, interpreting the average age-related risk as an individual risk) and is prone to comparing risks between age-groups. Women often fail to make a correct distinction between their average age-related risk and their own individual risk.\textsuperscript{16} Moreover, a more objective explanation of the age-related and estimated risk to younger women could stimulate equal access. It is not only the women who think that their age is the strongest predictor of their Down syndrome risk, but there is evidence that some healthcare professionals think the same and counsel accordingly.\textsuperscript{16,17,18}
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LEARNING CURVE AND EXPERIENCE

Chapter 4 shows that pregnancy losses after invasive procedures performed transabdominally or transcervically (by forceps) are lower than previously thought, provided they are performed by experienced operators. The fear of losing a wanted pregnancy is still one of the most important factors influencing women’s decision to opt or decline CVS or AP.

Chapter 4 confirms the impact of operator and procedure related characteristics on the procedure related risk of fetal loss, with fewer losses by experienced operators. This is in line with the study of Wijnberger et al. that emphasized the importance of the level of operator and center experience, irrespective of the technique used. Appropriate training of new operators under experienced supervision or by the use of training models, can minimize a learning curve effect. Furthermore there is a direct and positive relationship between operator caseload and sampling efficiency. This calls for centralization in only few centers by experienced operators, increasing the minimal caseload per year per operator. In the Netherlands, the Dutch society for Obstetrics and Gynecology has recommended a minimal number of 30 procedures per operator per year. However, there is no clear evidence that this number of procedures is sufficient to maintain and develop experience. Nor is it clear how many operators will still meet this requirement in view of the introduction of the cell free-DNA test and, consequently, the rapidly declining numbers of CVS and AP. This prompts for reconsideration of our national quality-norm. However it remains difficult to establish what the minimal number of procedures per year must be. One should be aware that operator’s competence is more than his/hers experience in terms of numbers performed alone and also depends on individual operator’s skills (e.g., the amount of repeated attempts). The RCOG states that an operator’s competence should be reviewed when fetal loss rates appear high and an audit should occur when the loss rate exceeds 4/100 consecutive amniocenteses or 8/100 consecutive CVS, but these criteria are based on expert opinion.

Increasing the minimal number of procedures per year per operator will most likely positively influence operator competency and patient safety, but it also compromises training of new specialists as well as the numbers of procedures needed to maintain operator competency. As a consequence, the development of an individual quality control program for invasive procedures could be considered, taking into account individual operator’s numbers, and safety. In other fields of medicine, especially in minimal invasive surgery, cumulative summation (CUSUM) analysis is used to assess the learning curve for certain procedures. CUSUM is a quantitative assessment of consecutive procedures and their outcome performed over a certain time interval, with reference to an agreed standard (for example, an expected complication rate). This could be an appropriate method to monitor learning curves for invasive procedures and set a standard for the minimal caseload per year per operator, but also to monitor the performance of experienced operators. Alternatively, the use of simulation models could be an effective strategy to train new operators and refresh and maintain experience of trained operators.

CURRENT PRENATAL SCREENINGS PROGRAM AND INTRODUCTION OF NIPT

In Chapter 3, 5 and 7 we examined the possibility to improve the detection rate of chromosomal and structural abnormalities in the first trimester of pregnancy. We show that
an increased NT is much more than just a marker for Down syndrome, since increased NT is also associated with other chromosomal abnormalities, structural anomalies, genetic syndromes, a higher risk of miscarriages and intrauterine death. Furthermore, facial markers can help to detect chromosomal and structural abnormalities in the first trimester. However, the role of first trimester ultrasound as screening test for Down syndrome and other chromosomal and genetic abnormalities, as described in Chapter 2-7, is likely to change with the recent preliminary decision of the Ministry of Health to make NIPT available as first tier screening for all women as part of the TRIDENT II Study.  

A study by Tamminga et al. showed that most healthcare professionals in the Netherlands (72%) think that NIPT should replace the CT, but almost half (43%) feels that the possibility of NT-measurement should be maintained. Internationally, the percentage of healthcare professionals in favor of maintaining the NT-measurement is even higher, 71%. 

In the Netherlands NIPT was introduced in April 2014, as part of the TRIDENT-I national implementation study. Dutch pregnant women were eligible for NIPT only when they had an increased risk after the CT (≥1:200), except when the NT was >p99, or when they had an increased risk based on their obstetric history. When it comes to detecting trisomy 21, NIPT has better screening characteristics than the CT, with a high sensitivity of 99% and a low false positive rate of < 0.1. As a result, the future of the CT as screening test for Down syndrome is uncertain since the test characteristics of the NIPT are by far better, it can be carried out from 10 weeks of gestation and onwards, and preliminary results of the TRIDENT-I study show that the number of invasive procedures is declining. 

The place NIPT is going to take in the Dutch prenatal screening program, as first or second tier test, is still a matter of debate. For TRIDENT II, the successor of the TRIDENT-I study, the Ministry of Health has granted a permission in July 2016, within the Population Screening Act, to carry on with NIPT and to extend the offer to all pregnant women as a first tier test. As a result, in the near future all women are allowed to choose between NIPT or the CT as first-tier screening test for trisomy 21, 18 and 13. In the TRIDENT II study, women who opt for the CT as first-tier test, can still later opt for NIPT when an increased risk is present (TRIDENT-I). When women opt for NIPT as first-tier test, the CT will be replaced (TRIDENT-II). 

Since NIPT has a higher detection rate for trisomy 21 and a lower false positive rate than CT, the likelihood of an unwanted invasive procedure is much lower. As a result, many Dutch women who were not eligible to the TRIDENT inclusion criteria, travelled abroad to undergo NIPT in centers offering NIPT commercially. This situation was the main incentive for the liberalization by the Ministry of Health, since it created a disparity between well informed women with a good financial situation and others in less fortunate circumstances. Despite the granted permission of the Ministry of Health, the financial aspects (who will be responsible for the costs; the women, the government or insurance companies) and the implications for equal access to the NIPT are unresolved at this moment. The Netherlands would be the first European country offering this new form of screening as a first tier test, implying that all women may choose to have it as first form of screening, followed by a confirmatory invasive procedure in case of a positive test. Other European countries use NIPT mainly as second tier test. One drawback of offering NIPT as first tier test, besides associated health care costs, is that it may result in a poorer detection of trisomy 13, trisomy 18, triploidy and sex chromosome
anomalies. Which are more efficiently detected by a contingent screening approach, i.e. CT followed by NIPT in case of high-risk.\textsuperscript{31,32}

While the Dutch laboratories are preparing to accommodate the expected rise in demand for NIPT, a Commission Prenatal Screening of the Health Council is working on a proposal for a future broad screening offer in pregnancy, not only confined to congenital anomalies, but also for other conditions, such as pre-eclampsia and premature labor.

One of the arguments against making NIPT available as 1st tier test to all women is the concern, shared by both healthcare professionals and women, that pregnant women would opt for the test too easily without having thought about the possible consequences.\textsuperscript{26} Interestingly, a Dutch study showed that 54\% of pregnant women did not think that NIPT would lead to more women feeling obliged or coerced to participate in screening.\textsuperscript{33} However to facilitate informed decision making regarding NIPT, as with the CT, adequate counseling is and remains a key-issue. In the Netherlands counseling is mainly performed by community midwives, and research suggests that 74\% of the counseled women make an informed choice regarding the CT.\textsuperscript{34} At this moment, counseling for NIPT is mainly performed by trained healthcare professionals in academic hospitals. When NIPT will be adopted as first-tier test, the counseling in primary care will mainly be performed by community midwives. To guarantee the quality of counseling for this more complex screening test, counselors will have to be trained. The National Center for Screening is already planning mandatory training workshops for 2017. Counseling has to cover the differences between NIPT and the CT, the predictive value of a positive NIPT test and the possibility of unexpected fetal or maternal findings. The difference between the micro array’s coverage and NIPT, in case of an increased NT > 3.5 mm or structural anomalies, should also be discussed. With increasing complexity of counseling, the expectation is that only a limited number of midwives specialized in prenatal counseling will perform the counseling. Also other options should be explored, like a decision aid or web-counseling.\textsuperscript{35}

Another concern is that when NIPT as 1st tier test is performed early in pregnancy, women become aware of an increased risk on a trisomy in early pregnancy, and they could be more likely to terminate the pregnancy. Some women and also some healthcare professionals think this could have a negative impact on the current social view on people with a handicap in society, in that they are less accepted in comparison to people without a handicap. However, reasons to terminate a pregnancy can be very diverse and may be independent from a woman’s view on existing handicapped people in society. When the pregnancy is wanted, women always experience the decision to terminate as a difficult one.\textsuperscript{36}

An important incentive whether or not the NIPT becomes a first or second-tier test is the impact on health care costs. A Dutch study by Beulen et al. showed that implementation of NIPT as second-tier test was the strategy with the lowest cost per case of trisomy 21 diagnosed, in comparison to current clinical practice or when NIPT was used as first-tier test, but this partially depended on the cost per NIPT-test.\textsuperscript{37} If the costs per NIPT-test decreased, it became feasible, in terms of health care costs, to introduce it as a first-tier test.

In case the Dutch laboratories will be able to offer the test at a lower cost, there will be no financial barrier to introduce NIPT as first tier test, although other than financial barriers may still exist. However, that leaves still three issues that need further consideration: The first one is that NIPT shows excellent performance for trisomy 21, relatively
good performance for trisomy 18, but definitely suboptimal performance for trisomy 13, Turner and Triploidy in comparison to the CT.\textsuperscript{10,32} The second one is that the Ministry of Health has agreed to counsel pregnant women whether they want to be informed on coincidental findings that may indicate other kind of pathologies, for example a still unknown maternal neoplastic disease.\textsuperscript{28,38} Although use of filters can eliminate these unexpected findings,\textsuperscript{29} above mentioned issues will make counseling of women even more challenging if all the nuances, limitations and coincidental findings have to be understood in light of making an informed decision, for both the caregiver and the women.

Thirdly, removal of the first trimester scan at 11-13 weeks from the prenatal screenings program and only including a dating scan before 10 weeks of gestation, prior to NIPT, would also forego the opportunity of early detection, since the first trimester scan has the potential to be more than just a risk calculation for chromosomal anomalies in the form of the CT (e.g. early detection of anencephaly, holoprosencephaly, hydrops, omphalocele, gastrochisis, body-stalk anomalies).\textsuperscript{39} This calls for a serious reconsideration of the role of first trimester ultrasound and the need of a possible early anomaly assessment, including the NT as marker of abnormal development.

In the Netherlands, 2-3\% of the children are born with a congenital anomaly, and 10\% of these children will have a chromosomal abnormality. At this moment NIPT is able to detect trisomies 21, 18 and 13, together around 50-60\% of all the numerical chromosomal anomalies. The majority of congenital fetal abnormalities, however, are structural anomalies\textsuperscript{40} that can be detected by first and/or second trimester ultrasound and not by NIPT. Beulen et al. showed that NIPT is not a valid alternative to conventional karyotyping or CGH-array for the evaluation of the etiology of structural anomalies, as microscopic aberration responsible for malformations cannot yet be picked-up by NIPT.\textsuperscript{41}

Since women in the Netherlands value screening for structural anomalies, we suggest all women should be counseled on the possibility of early diagnosis of structural anomalies by a scan around 12-13 weeks. NT-measurement should be part of this scan, in view of its value as marker of structural (especially congenital heart defects) and genetic disorders (especially Noonan syndrome), requiring referral to a Fetal Medicine Center and counseling on a genetic test with a broader coverage than NIPT.\textsuperscript{39,42} This is shown in Chapter 5 and 6. This possibility should be offered to all women, irrespective of their choice for NIPT.

Our research group has conducted a study on the 12-13 week anomaly scan with the primary aim to study which percentage of congenital anomalies are detected by ultrasound in the first trimester of pregnancy. Preliminary yet unpublished data indicate that a first trimester anomaly scan, performed by trained sonographers at the time of the CT, can identify about 45-50\% of the anomalies in an unselected population and 100\% of the trisomies. This is in line with previously published data.\textsuperscript{39} Especially severe anomalies in which parents should decide on the termination of pregnancy in more than 50\% of the cases, are detected. Furthermore, there is increasing evidence that at the first trimester scan individual risks can be predicted for a number of conditions such as pre-eclampsia, IUGR, preterm labor and gestational diabetes.\textsuperscript{43-45} Our research group is performing a study where we evaluate the ability to predict preeclampsia (PE) and growth restriction not associated with PE (GR) by using a risk assessment model based on existing algo-
rithms. The aim is to see whether early risk prediction for pre-eclampsia is feasible and valid, and if it is indeed, an implementation study could follow to see whether this could work as part of the national screening program in the Netherlands. The results of the ASPRE Study, an international multicenter study on the yield of first trimester screening for PE and consequent use of low-dose aspirin in the high-risk group, will shortly be known.\textsuperscript{46} It may well be that the first trimester assessment will lose its character of primarily screening for chromosomal anomalies and become, as already suggested in the literature for some time, the first and most important moment of a general risk assessment (care for low risk women by the midwife, or high risk women under care of the gynecologist) in pregnancy.\textsuperscript{45,47}

Based on the recent discussion on the general risk assessment during pregnancy in our Dutch system, characterized by midwives and gynecologists sharing the care of pregnant women, this new role of the first trimester assessment may revolutionize the model of care.

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