National implementation of the first-trimester anomaly scan: benefits, opportunities and challenges

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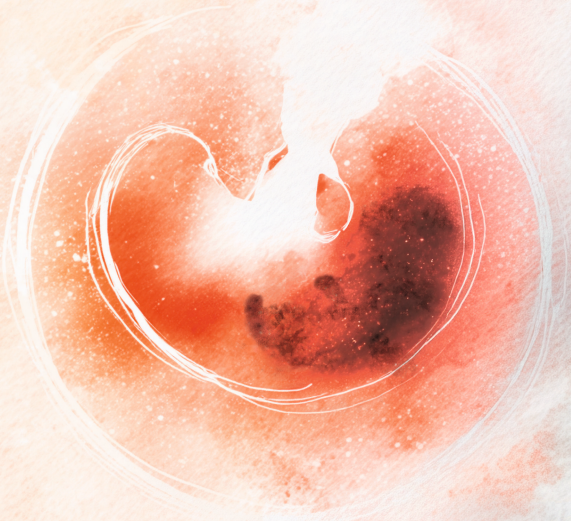

CHAPTER 1

General introduction

Prenatal screening in the Netherlands

The primary aim of the Dutch government-funded prenatal screening program for the detection of fetal anomalies is to provide future parents with reproductive autonomy. This means providing prospective parents with information for making informed reproductive choices.[1] In the Netherlands, prenatal screening is regulated by the Population Screening Act, which requires a governmental license from the Ministry of Health, Welfare and Sport. This legal framework aims to protect the population from potential harms caused by screening.[2, 3] The Dutch prenatal screening program includes first-trimester screening for aneuploidy, which was initially performed using the combined test, but has been gradually replaced by non-invasive prenatal testing (NIPT) since 2014. In addition, the program offers a second-trimester anomaly scan (SAS) for the detection of fetal structural anomalies. NIPT was first introduced into clinical practice in 2011.[4] In the Netherlands, NIPT became available in 2014 as part of the TRIDENT-1 study (Trial by Dutch laboratories for the evaluation of Non-Invasive Prenatal Testing) for which the Dutch NIPT consortium obtained a governmental license.[2] It was initially offered to pregnant women who were identified as having an increased risk based on the first-trimester combined test.[5] Since 2017, NIPT is available as a first-tier screening test for aneuploidy for all pregnant women.[5] It has replaced the combined test in the Netherlands in 2021 due to its superior test characteristics and the declining uptake of the combined test.[6, 7] An out-of-pocket payment of €175 was required for NIPT, but since April 2023, NIPT has been offered free of charge.[5, 8] The SAS was introduced into the Dutch prenatal screening program in 2007, originally aimed at screening for neural tube defects. It is performed between 18 and 21 weeks of gestation, preferably between 19 and 20 weeks, and is reimbursed by the government.[9] When an anomaly is suspected, parents are referred to a tertiary care centre, where a detailed diagnostic scan is performed and additional (genetic) tests may be conducted. Subsequently, counselling is provided regarding the diagnosis and prognosis, and a management plan is discussed.

Rationale

Congenital anomalies are diagnosed in 2.5% of all births in the European union.[10] Prenatal ultrasound has developed enormously, resulting in a significant improvement of image resolution.[11] There is increasing evidence that a significant proportion of fetal anomalies identified during the SAS can already be detected in the first trimester, with reported detection rates of severe congenital anomalies varying between 32% in low-risk populations to 61% in high-risk groups.[12, 13] Timely diagnosis provides parents with more time for reproductive decision-making. Despite this, the Dutch Health Council was unable to advise the government on the implementation of a first-trimester anomaly scan (FTAS) in the Netherlands, because the added value of a nationwide FTAS is

uncertain.[14] Therefore, the Health Council advised the government in 2016 to initiate a nationwide study to generate more evidence on the added value of an FTAS into the existing prenatal screening program and to explore all relevant implementation aspects. In contrast to other countries where the FTAS is introduced gradually, in many occasions without a national protocol, the Dutch setting offers a distinctive context for evaluating FTAS implementation and for comparing the situation without the FTAS to one in which the FTAS is integrated into the national screening program.

IMITAS study

The FTAS was introduced into the Dutch prenatal screening program in September 2021 as part of the nationwide 'Implementation of first Trimester Anomaly Scan' (IMITAS) study, aiming to detect major congenital anomalies earlier in pregnancy.[15] Apart from the prenatal screening program, a viability scan is offered in the first trimester when indicated, and a dating scan takes place between 10 and 12+6 weeks' gestation as part of routine obstetric care.[16] Prenatal screening in the Netherlands is unique in the world due to its centralized organization, coordinated by the Centre for Population Screening of the Dutch Institute for Public Health and Environment (RIVM). This national structure ensures standardized screening protocols, uniform training of counsellors and sonographers, mandatory certification and systematic quality monitoring.[17]

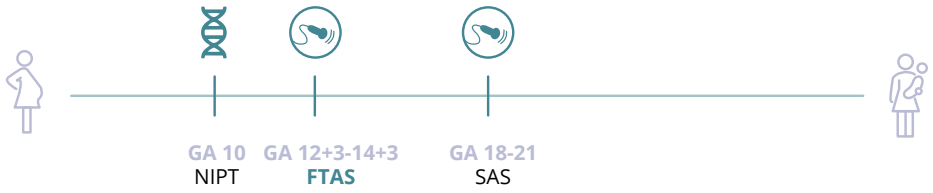

Figure 1. Prenatal screening program in the Netherlands

Abbreviations: FTAS, first-trimester anomaly scan; NIPT, non-invasive prenatal testing; SAS, second-trimester anomaly scan.

Potential benefits of the FTAS include:

1. **Additional diagnostic yield**
   Structural fetal anatomical screening in the Netherlands is limited to the SAS. While routine scans in the first trimester can sometimes detect major anomalies as well, implementing the FTAS would allow earlier and more accurate detection of these and similar severe defects.

2. **More time for evaluation**
   Earlier diagnosis through an FTAS allows more time for genetic testing, additional scans or consultation with specialists. Furthermore, it could provide parents with more time to consider their options and thus increase reproductive autonomy.

3. **Earlier termination of pregnancy**
   It has been suggested that termination of pregnancy (TOP) at an earlier GA has less psychological impact.[18-20] After an abnormal FTAS, parents could opt for TOP earlier in pregnancy.

Potential disadvantages of the FTAS include:

1. **Prolonged diagnostic trajectory**
   FTAS introduction might lead to referrals in which a precise diagnosis cannot be made upon arrival in the tertiary care centre. This could lead to follow-up scans, waiting time and additional diagnostic tests, before a definitive diagnose can be made. If the diagnosis becomes only evident towards mid-gestation, the FTAS has no additional benefit. Yet, it prolongs the diagnostic trajectory and could cause anxiety and uncertainty.

2. **False-positive findings**
   FTAS may result in false-positive findings, consisting of referrals with normal findings in the tertiary care centre or transient findings that resolve spontaneously later in pregnancy (e.g. small omphalocele, megabladder, increased nuchal translucency in euploid fetuses). These findings may cause parental anxiety or influence decision regarding TOP.

3. **False reassurance**
   The detection rate for all anomalies detected by first-trimester ultrasound in low-risk or unselected populations is 32.4% according to a review by Karim et

al.[12] The psychological impact on pregnant women who had a normal FTAS, but abnormal SAS is unknown.

4. **Mistaken belief that the FTAS preempts aneuploidy screening**
   NIPT required an out-of-pocket payment until April 1st, 2023. The introduction of the FTAS may have influenced women's decisions regarding NIPT. Some may have decided to decline NIPT based on the mistaken assumption that the FTAS alone is sufficient to detect aneuploidies, leading to false reassurance.

Knowledge gaps

There are three main domains of knowledge gaps that must be assessed, as well as a pre-defined framework in which the IMITAS study needs to be performed. The pre-defined framework includes a nationwide simultaneous introduction of the FTAS to all pregnant women in the Netherlands in 2021 and the study must address all knowledge gaps including an ethical analysis.

The most important defined knowledge gaps are:

1. **Uptake and test performance**
   It remains unknown if the test performance of the FTAS maintains as good as previously reported[21] when performed by primary care sonographers. The only Dutch experience with FTAS is limited to a study conducted in six high-volume ultrasound practices by motivated and experienced sonographers, which may not reflect clinical practice in other parts of the country.[22] Furthermore, there are no uptake rates available if the FTAS is offered nationwide as part of the national screening program. To assess potential disadvantages of widespread implementation, several factors must be evaluated, such as the number of subsequent referrals to tertiary care centres, the number and types of healthcare professionals involved, the number and nature of additional diagnostic tests performed, the time to reach a final prenatal diagnosis and the incidence of pregnancy termination following FTAS findings.

2. **Women and partners' perspectives**
   The decision-making process, perspectives and preferences of women and their partners regarding the FTAS, particularly in the context of other prenatal screening options, is unknown. Evidence is limited on the psychological impact of the FTAS, including anxiety related to false-positive results, false reassurance and the uncertainty of prolonged diagnostic trajectories. These aspects require further investigation, especially given the primary aim of the Dutch prenatal screening

program: to support informed reproductive choices. Although the majority of women are expected to opt for the FTAS, it is unknown whether the anticipated benefit of an earlier gestational age at TOP outweighs the psychological burden of receiving a diagnosis later in pregnancy following repeated follow-up scans.

3. **Aspects of implementation and embedding in obstetric care**
   a. **Perspectives of professionals**
      The perspectives of the different professionals involved in prenatal care are crucial in weighing the final decision on whether and how to implement the FTAS. It is unknown whether they feel competent in diagnosing anomalies in the first trimester and whether a prognosis can be provided. These aspects have not previously been investigated.

   b. **Different scenarios for future implementation**
      The optimal conditions for early detection of fetal anomalies have not yet been systematically assessed. While this may be achieved through the FTAS, it is also possible that the dating scan already provides sufficient detection of (major) anomalies. Furthermore, the timing of the FTAS in relation to other prenatal tests, such as NIPT, is unknown.

4. **Ethical considerations**

Aim and research questions

The main objective is to evaluate all relevant aspects of FTAS implementation into the Dutch prenatal screening program. An additional aim of the IMITAS study is to provide insight into the balance between benefits and potential harm of the FTAS.

The research questions as formulated by the Health Council, ZonMw and RIVM are depicted in Table 1.[23]

Table 1. Research framework of FTAS implementation[23]

Part I: Uptake and test performance	
I.1	What proportion of pregnant women receive information and counselling regarding the FTAS? What proportion of women opt for the FTAS following information and counselling?
I.2	What proportion of pregnant women receive an abnormal FTAS result? What proportion of abnormal FTAS results are confirmed and which anomalies are identified? In what proportion of cases is the FTAS incomplete?
I.3	What follow-up tests are required after an abnormal FTAS? What is the time to a final prenatal diagnosis following referral? How does this compare to diagnostic trajectories following the SAS (without a preceding FTAS)?

Table 1. (Continued)

Part I: Uptake and test performance	
I.4	What are the test characteristics (e.g., sensitivity, specificity, positive predictive value) of the FTAS? What other findings are identified during the FTAS and how reliable are these findings?
I.5	What is the number of referrals to a tertiary care centre following an abnormal FTAS result and how many pregnancies are terminated as a result of an abnormal FTAS? How do these numbers compare to referrals and pregnancy terminations following an abnormal SAS?
I.6	How frequently is the FTAS performed using transvaginal ultrasound? What are the reasons for choosing a transvaginal approach? What are the outcomes—in terms of detecting anomalies and pregnant women's experiences—compared to abdominal ultrasound, which is typically the standard method?
Part II: Women and partners' perspectives	
II.1	What reasons do pregnant women and their partners report for opting for the FTAS? Conversely, what reasons do they provide for not opting for the FTAS?
II.2	What are the experiences of pregnant women and their partners with prenatal counselling related to the FTAS?
II.3	To what extent are pregnant women and their partners satisfied with FTAS? If relevant, assess satisfaction at multiple time points, such as immediately after the FTAS, following additional testing if applicable and postpartum.
II.4	How do pregnant women and their partners perceive the frequency of obstetric care during the first trimester of pregnancy?
II.5	How do women with previous pregnancies and their partners evaluate the FTAS in comparison to the prenatal screening and care offered during their earlier pregnancies?
II.6	What are the experiences of pregnant women and their partners in relation to a normal or abnormal FTAS and whether or not those findings are confirmed?
II.7	What are the experiences of pregnant women and their partners who, following an abnormal FTAS, did or did not opted for pregnancy termination? How do these experiences compare to women who made similar decisions following an abnormal SAS?
Part III: Aspects of implementation and embedding in obstetric care	
III.1	What are the experiences of healthcare professionals (e.g. midwives, obstetricians, sonographers, clinical geneticists) with FTAS implementation? What effects on the quality of obstetric care are perceived or anticipated as a result of the FTAS?
III.2	What are the effects of the FTAS on the dating scan, screening for Down, Edwards, and Patau syndromes and the SAS? Consider aspects such as uptake, prenatal counselling, organization, and the order of prenatal screening tests. Investigate, for example at a regional level, whether and under what conditions combining the dating scan with the FTAS is feasible.
III.3	If necessary, how might the SAS be adjusted if the FTAS would be implemented?
Part IV: Ethical considerations	
IV.1	How does the addition of FTAS affect the benefit to harm ratio of prenatal screening offer as a whole, for those to whom it is offered?
IV.2	To what extent does the addition of this extra test fit in with the aim of the program of prenatal screening for fetal anomalies?
IV.3	How should the addition of this extra test be assessed from the perspective of the wider ethical and societal debate about the acceptability of prenatal screening?

Abbreviations: FTAS, first-trimester anomaly scan; SAS, second-trimester anomaly scan.

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AIMS AND OUTLINE OF THIS THESIS

All aspects are extremely relevant in the overall assessment of the FTAS, yet this thesis focuses on the uptake and test performance of the FTAS and women's experiences regarding abnormal screening results.

Chapter 2 shows an overview of the current practice of first-trimester ultrasound screening for structural fetal anomalies in developed countries. In **chapter 3**, the uptake and test performance of the FTAS in the Netherlands is presented during its first year of implementation. These findings are compared to the situation before FTAS implementation in **chapter 4**, to assess the value of the FTAS in routine care on population level to the yield of routine scans only on key outcomes such as time to prenatal diagnosis. In **chapter 5**, we examined the undetected cases after the FTAS and explored reasons why these cases remained undetected by studying all scan reports and images of a specific group of undetected anomalies. To evaluate the FTAS results in the broader context of first-trimester anomaly detection, the potential of the dating scan, in terms of the detection of major structural anomalies, was evaluated in **chapter 6**. In **chapter 7**, the psychological impact of an abnormal screening scan on maternal well-being is assessed. The results of a mixed-methods study evaluating the psychological impact and perspectives associated with early versus late TOP are described in **chapter 8**.

This thesis concludes with an in-depth discussion of the main findings.

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