IMITAS STUDY: ETHICAL CONSIDERATIONS

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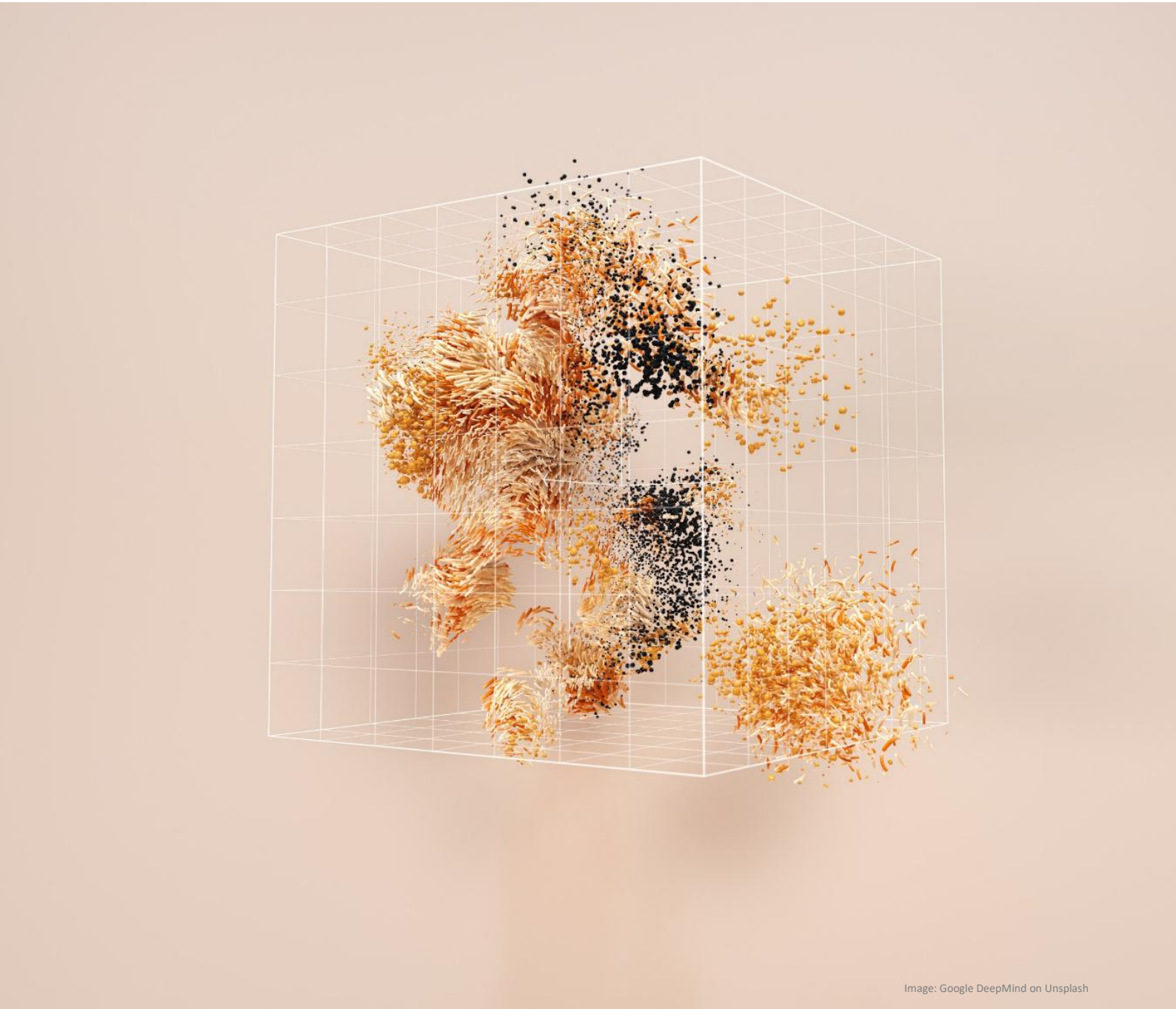

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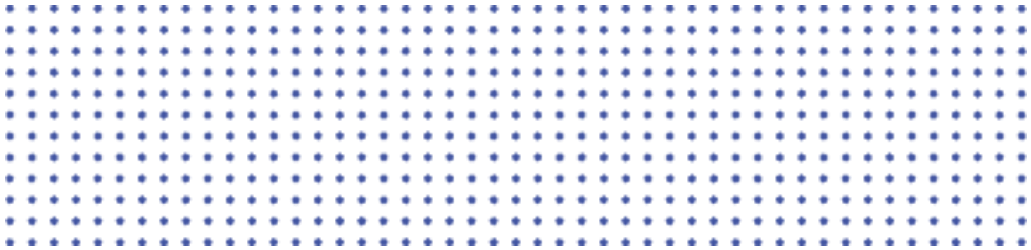
Preface

In this report, as part of the ZonMw IMITAS study, the pros and cons of adding a first-trimester anomaly scan to the Dutch national prenatal screening program for fetal abnormalities will be considered from an ethics perspective.

Apart from the relevant literature, we used data and documents from the IMITAS study for this report. This includes a published paper on core results of screening with a first-trimester anomaly scan in the research period (Nov 2021-Nov 2022) [1], as well as the July 2024 Interim Report [2], papers in preparation [3, 4], further unpublished data, and interview transcripts. Earlier versions of this document were discussed with the project leaders (prof. dr. M.C. Haak, LUMC, Leiden and prof. dr. M.N. Bekker, UMCU, Utrecht) of the IMITAS study.



Content

1. Introduction

The pros and cons of adding a first-trimester anomaly scan to the Dutch national Prenatal screening program for fetal abnormalities will be considered from an ethics perspective, taking account of the existing normative framework for (prenatal) screening.

After this introductory section, we use the elements of the normative framework (see section 1.3) to further structure our discussion. In the final section, we present our conclusions and list our recommendations.

1.1 The place of ultrasound in the current prenatal screening program

The present prenatal screening program, consisting of first-trimester screening for chromosome abnormalities and second-trimester ultrasound screening for structural abnormalities, was introduced in 2007. The Dutch screening program is unique in the world because of its centralized set-up, with a national protocol, a quality monitoring system and mandatory training for counselors and ultrasonographers. The Center for Population Screening of the National Institute for Public Health and the Environment (RIVM-CvB) directs and manages the program on behalf of the Minister of Health, Welfare & Sport.

An important impetus for the multidisciplinary collaboration and efforts that led to this globally acknowledged high-quality screening program was the equally unique legal framework of the Dutch Population Screening Act (Wet op het bevolkingsonderzoek), aimed at protecting the population against physical or psychological risks of population screening.[5, 6] This includes the requirement of a government license for any screening initiative targeting conditions for which no options for treatment or prevention are available.[3] As from the coming into force of the Act in 1996, this meant that prenatal screening for fetal abnormalities was considered to require a license, for which the Act requires the government to seek advice from the Health Council of the Netherlands.

In the early days of the program, the screening for chromosome abnormalities was licensed for trisomy 21 (Down syndrome) only. In 2010 it was expanded to include trisomies 13 (Patau syndrome) and 18 (Edwards syndrome). For this screening, the first-trimester 'Combined Test' was used: a risk estimation based on biochemical markers in the pregnant woman's blood, combined with her age and an ultrasound scan measuring the thickness of fluid at the base of the neck of the fetus (nuchal translucency; NT-measurement). Since late 2021 the Combined Test is no longer in use; it has been replaced by the more accurate Non-Invasive Prenatal Test (NIPT) based on analysis of cell-free DNA in the maternal circulation, in which there is no longer a role for NT-measurement.

[3] For the purpose of the Act, termination of pregnancy is not considered a form of prevention. Wet op het bevolkingsonderzoek. Memorie van antwoord. Kamerstukken II 1990-91, 21 264, nr. 5.

After having been available in a six-year nationwide study[4], NIPT was formally introduced on 1 April 2023[5].[7] In 2023, the Health Council has advised to broaden the scope of the screening with NIPT[6] to also include large structural chromosome abnormalities, consisting of deletions and duplications of parts of chromosomes, while still excluding the sex chromosomes from the analysis.[10, 11] The Minister has followed the Health Council's advice[7]; the new situation will be implemented as from 1 April 2025.[8]

Whereas earlier forms of screening for chromosome abnormalities (age-based screening; triple test screening) preceded the current program, ultrasound screening with the Second-Trimester Anomaly Scan (STAS), together with a recommended obstetric 'dating scan' at the start of midwifery or obstetric care, was meant to put an end to the widespread practice of 'wild' scanning, as a result of which 90% of pregnant women in the late 1990s had at least one scan during pregnancy. Due to the uncoordinated nature of these scans, and given the termination limit at 24 weeks of gestation (see section 3.1), women were often referred too late to allow for a timely diagnosis of conditions for which they might had considered a termination of pregnancy.[12]

At the start of the program in 2007, screening with STAS was formally licensed for neural-tube defects only. This was based on the reasoning in consecutive Health Council reports that only as a screening test for those conditions[9], ultrasound screening had a demonstrable positive benefits-to-harms ratio, given the combination of good test characteristics and a high percentage of women or couples considering a termination of pregnancy for this condition.[12-14] For other conditions detected with ultrasound screening, no such conclusion could be drawn. And while at the time there were 'indications' that ultrasound screening might also improve the postnatal prognosis of certain conditions as a result of adapted obstetric management, these were not considered sufficiently robust to provide a further justification for screening[10].[12]

[4] In the TRIDENT-2 study, starting 1 April 2017, women opting to have prenatal screening for fetal abnormalities could choose between having the first-trimester Combined Test or NIPT. Because the overwhelming majority of women chose NIPT, the use of the Combined Test was discontinued on 1 October 2021.

[5] Ruling of the Minister of Health, Welfare & Sport of 21 February 2023. Published Stcrt.2023, 6586.

[6] Because for the TRIDENT-2 study, a genome-wide form of NIPT was used that looks for abnormalities in all chromosomes except for the sex chromosomes, women opting for screening with NIPT were given the further choice to also be informed about secondary findings beyond the three common trisomies.[8] This meant a *de facto* enlargement of the scope of the screening.[9]

[7] Kamerbrief over Besluitvorming over GR-advies Wbo-vergunning voor de NIPT als bevolkingsonderzoek. 26 oktober 2023. Kamerstukken II, 29 323, nr. 176.

[8] As announced by the State Secretary of Health, Welfare & Sport in his statement of 4 November 2024. Published Stcrt 2024, 36650.

[9] More specifically spina bifida – other neural-tube defects such as anencephaly being already found in most cases with a first-trimester dating scan.[12]

[10] The Health Council's 2007 advice to license the program as screening for Down syndrome (with the Combined Test) and neural tube defects (with STAS), recommended systematic data collection on other conditions being found with ultrasound screening, in order to provide a basis for expanding the licensed scope of this part of the program.[14] In 2016, a further Health Council report stated that in the light of new data with regard to detection of and termination for severe cardiac abnormalities, those conditions were eligible for inclusion in the licensed scope of STAS.[15]

Of course, STAS inevitably finds structural abnormalities other than neural-tube defects. Moreover, as from the start of the program, professional guidance was established for ultrasonographers regarding referrals also for other abnormal sonographic findings, meaning that *de facto*, the STAS has always been a much wider screening test than only for neural-tube defects. This was acknowledged by the State Secretary of Health, Welfare & Sport in his decision-making about the IMITAS study. He decided to solve the problem by removing any qualification of the licensed scope of STAS, thus effectively, and without further debate, broadening this screening to whatever anomalies the scan might reveal[11].

1.2 Introduction of first-trimester ultrasound screening in a research setting

There is increasing evidence that a large proportion of major structural anomalies seen with STAS, can already be detected in the first-trimester.[16] Earlier detection of those conditions might have important benefits: more time for follow-up testing, more time for decision-making, earlier intervention, lower gestational age at termination coming with less emotional impact. But, in addition to extra costs in terms of finances and other resources, there may also be drawbacks that have to be considered, such as false positives and extended uncertainty, the burden of an additional screening test, and a general concern that early scanning might lead to more terminations, even for less severe abnormalities.

In 2016 the Health Council advised the Dutch government to initiate a nationwide study to gather more evidence on the added value of a first-trimester anomaly scan (FTAS) in the current screening program and to explore all relevant implementation aspects.[15] This led to the ZonMw financed IMITAS study[12] in which all pregnant women in the Netherlands were offered the option of having FTAS between 12+3 and 14+3 weeks of gestation, as a further ultrasound screening test in addition to STAS, starting 1 September 2021.

IMITAS is a prospective cohort study, with data collected from two cohorts. In the BEFORE cohort, data were gathered during 8 months prior to the introduction of FTAS, thus providing researchers with a benchmark situation in which STAS (at 18-20 weeks of gestation) was the only ultrasound scan offered as a prenatal screening test. For the AFTER cohort, data about the impact of and experiences with FTAS were collected in the first year after its introduction as a further screening test in the program. Apart from data collection about test performance, the study included surveys exploring experiences and attitudes of participating and non-participating women and their

[11] Ruling of the State Secretary of Health, Welfare & Sport of 13 July 2024. Published Stcrt. 2021, 44766. In his decision granting a research license for the IMITAS study, the State Secretary considered that as a matter of fact, STAS is also used to screen for other anomalies than neural-tube defects, and stated that in the current license for the program as a whole (as renewed in 2020), the qualification “for neural-tube defects” had to be erased from all references to STAS.
[12] Acronym for: IMplementation of fIrst-Trimester Anomaly Scan. ZonMw grant number 543010001.

partners, as well as of professionals, plus in-depth interviews among women who chose to have their pregnancies terminated because of a fetal abnormality. After the end of the study, FTAS remains on offer under an extended research license, pending further decision-making about its possible place in the prenatal screening program.[13]

For the IMITAS study, a protocol for ultrasonographers was drawn up by a project group of the RIVM-CvB in close collaboration with the Regional Centers for Prenatal Screening and relevant professional societies.[14] In the period preceding the study, FTAS-ultrasonographers were trained to work with this. The protocol specifies which anatomic and biometric structures they must assess and how, and what findings they must refer as suspected fetal anomalies for confirmatory diagnostic testing. In its advisory report recommending the granting of a research license for the IMITAS study under the Population Screening Act, the Health Council has commented on this.[17] According to the report, the broad scope of the protocol may generate many uncertain or clinically non-relevant findings, as well as follow-up testing that in hindsight may turn out to have been unnecessary. While the committee finds it important to as much as possible avoid such findings in a screening context, it acknowledges that the extended IMITAS-protocol was drawn up precisely for the purpose of research aimed at determining whether and on the basis of what protocol FTAS may have added value.[17]

As stated above, NT-measurement, the assessment of the size of a transient subcutaneous fluid collection visible at the end of the first-trimester, is no longer performed in the context of screening for chromosome abnormalities. However, when visualized on routine obstetric check-ups, an enlarged NT remained an indication for referral for an advanced diagnostic ultrasound scan, also due to its association with structural anomalies, for example cardiovascular anomalies.[18]

This 'sonomarker' has now returned as part of the FTAS-protocol, where NT must be measured by the ultrasonographer; an enlarged NT ≥3.5mm needs to be referred for diagnostic testing. The risk of abnormalities increases with the size of the NT, with "an extremely high chance of a favorable outcome" for euploid fetuses when initially NT is <4 mm.[19] The literature further shows that the majority of fetuses with NT ≥3.5 mm are normal, and of those that are abnormal, the majority are chromosomally abnormal, half of which are fetuses with Down syndrome that could be detected by NIPT.[20-22] In chromosomally normal (euploid) fetuses, NT ≥3.5 mm comes with a higher risk of a range of other serious conditions, including cardiac abnormalities and several genetic syndromes (such as Noonan syndrome), and is therefore an indication for follow-up testing with advanced

[13] Brief van de Staatsecretaris voor jeugd, Preventie & Sport aan de voorzitter van de Gezondheidsraad dd 24 juli 2024. The extension runs until 1 Juli 2026.
[14] RIVM, Pre- en neonatale screeningen (PNS). Kwaliteitsbeoordeling eerste trimester SEO. https://www.pns.nl/professionals/nipt-seo/seo/eerste-trimester-seo/voorwaarden/kwaliteitsbeoordeling-eerste-trimester-seo

ultrasound and/or whole exome sequencing (WES).[15] As increased NT is a transient phenomenon that resolves after 14 weeks of gestation, it is perfectly visible with FTAS, but usually no longer at the time of STAS.

1.3 Normative framework

Population screening is an offer of medical testing for latent disease, or a hereditary predisposition for disease, or risk factors for developing disease, to individuals in a group of otherwise healthy persons without a prior medical indication for having that test, with the aim of achieving health gains or other health related benefits through timely and effective interventions.[25] Prenatal screening is a special case, as it involves testing of pregnant women either with the aim of improving the health outcomes of their pregnancies, or – in case of fetal abnormalities for which therapeutic interventions are not available – to enable them to timely make an autonomous decision between continuing or terminating the pregnancy. These two aims are referred to as the 'prevention' and 'autonomy' aims of prenatal screening, respectively.[26]

While population screening can thus be beneficial, it can also cause harm and so a decision must be made whether specific screening is worthwhile, weighing the harms and benefits. Internationally, there is a broad consensus regarding the basic criteria that responsible screening should meet, based on the Wilson and Jungner screening principles published by the World Health Organization (WHO) as early as 1968.[27] These were summarized by the Health Council of the Netherlands, [15, 25] in the following terms:

- Screening must concern an important health problem (or health problems);
- it must be established that early detection through screening leads to significant health benefits or other meaningful outcomes for participants in relation to the health problem(s) targeted in the program; these benefits must clearly outweigh the harms that screening may also entail for them;
- participation in screening and follow-up tests must be voluntary and based on informed choice;
- the screening method must be scientifically proven and the quality of the various parts of the screening process must be guaranteed;
- the program must be justifiable in terms of cost-effectiveness and justice.

These conditions will be used to structure the next sections (2-7) of this part of the IMITAS report.

[15] When NT-measurement was done as part of the Combined Test for Down syndrome and other trisomies, the finding of an enlarged NT in a euploid fetus was an incidental finding of a risk factor for serious disorders outside the scope of the screening. When the introduction of NIPT as a better screening test for chromosome abnormalities made NT-measurement obsolete in that context, several prenatal care professionals regarded this as a loss, as the relevant conditions would not be found with NIPT and most likely also be missed with STAS.[23, 24]

2. Important health problem

Precisely because screening comes with drawbacks and costs, it is important that it should be targeted to conditions that are considered important health problems. This is not to say that it must be an important problem from a public health perspective due to a high prevalence in the population. The classical example here, already brought up by Wilson and Junger, is neonatal screening for phenylketonuria (PKU): "extremely uncommon, but warrants screening on account of the very serious consequences of not discovered and treated very early in life."[27] As suggested by the Health Council, in a review of updates of the Wilson and Jungner criteria, 'important' can both be a matter of prevalence and seriousness.[25]

2.1 Target conditions for prenatal ultrasound screening

There are no objective grounds for determining what constitutes a 'serious' health problem, as subjective assessments, experiences and perspectives (patient, parental, professional) inevitably play a role.[28] This does not mean that the distinction between serious and non-serious or between severe and mild (we use these terms interchangeably), is meaningless, since to a large extent it may still be possible to find intersubjective and context-dependent agreement among professionals and patients, based on an assessment of the (combined) impact of different disease characteristics (e.g. life expectancy, intellectual disability, types of impairment). Efforts in this direction have for instance been undertaken for genetic disorders with an eye to defining test panels for expanded preconception carrier screening.[29, 30]

Also in the context of expanded preconception carrier screening, researchers on 'Mackenzie's Mission', an Australian research project, have proposed two material criteria for what to include in the test panel for such screening.[31] Relevant disorders or conditions are either (a) of a nature where "an 'average' couple would take steps to avoid the birth of a child with that condition", or (b) where there is "potential benefit from knowing about the condition to inform management in the neonatal period". The first criterion would cover "conditions with lethality in childhood, [conditions] which are significantly disabling (…), or otherwise have a severe impact on quality of life for an affected child and significant negative impact on the family."

Mutatis mutandis, and with a slightly different phrasing, similar criteria may help distinguishing between proper target conditions and other findings of prenatal ultrasound screening. Here, as we propose, target conditions are either (a) such that many women/couples would want to be enabled to make an informed and timely decision between terminating the pregnancy and preparing for a child with special needs, or (b) such that timely perinatal intervention can significantly improve the the health outcome of the pregnancy.

With regard to the structural (morphological) anomalies that prenatal ultrasound brings to light, a distinction is usually made between major and minor anomalies, also based on differential health impact. As defined by Hennekam et al. major structural anomalies are those that have "a significant consequence for health or appearance at the time of evaluation, or had this in the past or will have it in the future", whereas minor anomalies have "minimal, or no, health consequence but may have a modest impact on appearance."[32]

In addition to structural anomalies, genetic (including chromosomal) and 'other' anomalies are two further main categories of findings of prenatal ultrasound. Genetic anomalies either come to light with both STAS and FTAS, when structural findings turn out to be part of a syndrome with a genetic cause, or after referrals because of an enlarged NT with FTAS. The 'other' category consists of findings such as sonomarkers, placenta anomalies growth related findings (abnormal biometry).

In each of these (overlapping) categories, it is inevitable that part of the findings have no, limited or uncertain clinical significance. While adding to the number of diagnostic procedures, as well to the material and immaterial (psychological) costs of the screening, these outcomes do not meaningfully affect pregnancy outcomes. In terms of the above criteria, they fall outside the intended scope of the screening.

2.2 Autonomy aim: 'all about choice'?

The notion that prenatal screening should be limited to (what are intersubjectively understood as) important health problems has been criticized as at odds with its autonomy aim (Stapleton 2016). In this connection, reference is often made to the consistent finding that many pregnant women who come for prenatal screening want to be informed about all abnormal outcomes that the test can reveal, including information about minor conditions or results with uncertain implications.[33-35] If this is what they want, and if the aim is to enable them to make autonomous reproductive choices, then why the limitation to important health problems? As has been argued: "If it is all about choice, then, no option or information potentially relevant to a woman's choice and her decision-making processes should be withheld".[36]

The problem with this reasoning is that it changes prenatal screening from a public health service aimed at securing collectively shared health related reproductive interests of future parents, to a mere information tool aimed at catering to individual reproductive preferences. Especially where prenatal screening, including ultrasound, is offered and funded in a public health context, as is the case in the Netherlands, the delineation of its scope must take account of harms and costs and therefore cannot simply be left to individual participants.[37]

Nor is it true that deferring this to those having screening is what the autonomy aim would require. To suggest that it would, ignores the context of the international ethical debate of the 1980s and 1990s from which this understanding of the aim of prenatal screening for fetal abnormalities has emerged as an alternative for prevention.[6, 26] This was the debate about whether prenatal screening could be morally justified when offered for conditions such as down syndrome or neural tube defects, conditions where a positive diagnosis would provide women with no other options but a choice between terminating the pregnancy or preparing for a child with special needs. The question at the time was how offering such screening would fit the traditional Wilson and Jungner criteria, that only spoke of benefits in the sense of population level health gains. It was widely felt that to regard selective terminations in the same light, would lead into the murky waters of eugenics and might put pressure on pregnant women so as to spare society the costs of expensive lives.[6, 25, 38]

The consensus from this debate was that prenatal screening for the relevant conditions could only be justified if aimed at serving reproductive autonomy, and the screening criteria were adapted accordingly.[39, 40] The idea behind this notion was not that prenatal screening should try to maximize autonomous choices as an aim in itself. On that understanding, screening should also be offered for fetal sex to those preferring to have either boys or girls, to name just one example of what maximizing reproductive autonomy might entail.[37] Rather it was that pregnant women should be enabled to determine for themselves whether the prospect of a child with possibly extensive medical needs was something they could accept or would rather choose to avoid. By leaving the scope of the screening offer confined to important health problems, this understanding of the autonomy aim is not at odds with offering prenatal screening in a public health context.

2.3 Reducing unsolicited findings

For ultrasound screening, this entails limiting its scope to major structural anomalies and other serious conditions.[16] Findings with limited or uncertain clinical significance are unsolicited and should ideally be avoided. However, whereas genome-wide prenatal (or preconception) screening for genetic or chromosome abnormalities can make use of bioinformatic filters or tests targeted at specific conditions so as to avoid the generation of unsolicited information, things are more complicated where ultrasound screening is concerned, as the whole fetus (whose movements in the uterus are beyond external control) will generally be seen by the ultrasonographer.

As suggested by the Health Council (see section 1.2), one conceivable (but limited) form of filtering is to adapt the protocol that specifies the anatomic and biometric assessments to be made by the

[16] On this point, the current license for screening with STAS seems to be in need of specification (see footnote 11; see also section 6.1).

ultrasonographer and what findings to refer as suspected fetal anomalies.[17] By excluding specific measurements more prone to lead to unsolicited findings or false positives, it is possible to at least avoid part of the challenges that come with such outcomes. Also, for ultrasound screening in the first-trimester (FTAS), an alternative option is to move the scan to an earlier gestational age, at which certain abnormalities (e.g. cardiac malformations) cannot yet be seen, because the fetus is still too small. Both approaches inevitably involve a trade-off in which avoiding unsolicited information comes at the price of a lower yield of targeted conditions. Finally, whereas in the context of prenatal screening for genetic or chromosomal abnormalities it is still possible to decide (as a matter of policy) not to report certain unsolicited findings included in the test result, no such strategy is conceivable with ultrasound screening, given the role and responsibility of the ultrasonographers, who are trained to see abnormalities, but not to assess them.

3. Benefits and harms of prenatal ultrasound screening

In this section, we provide a brief overview of what is known about benefits and harms of prenatal ultrasound screening generally. In the next section we will use this background to discuss whether adding FTAS to the present program would on balance be beneficial or harmful, based on the outcomes if the IMITAS study.

3.1 Benefits of prenatal ultrasound screening

Prenatal ultrasound screening may lead to benefits of two kinds: health benefits (prevention) and reproductive options (autonomy). Health benefits are achieved where anomalies are found that allow for timely and effective perinatal intervention. Here one should think of monitoring, medication or other forms of fetal treatment, induction of labor, or birth in a center where specialized surgery or other therapeutic interventions can immediately be performed postnatally. Although it seems reasonable to suspect that by enabling these measures, prenatal ultrasound in the first and/or second-trimester positively affects the health outcomes of pregnancies, this could not be confirmed in the latest Cochrane review. However, the authors point out that their review "may underestimate the effect in modern practice, because trials were mostly from relatively early in the development of the technology, and many control participants also had scans".[41] [17]

Most abnormalities that are brought to light by prenatal ultrasound are not (yet) amenable for interventions that may improve the health outcome of the pregnancy. Screening for these conditions can only be justified in view of other benefits, more precisely the information and connected reproductive options that a timely diagnosis of a serious abnormality makes available for pregnant women (and their partners). Taking account of the legal limit for a termination of pregnancy in the Netherlands, a timely diagnosis provides them with the choice between preparing themselves for the birth of a child with special needs, or asking for the pregnancy to be terminated.

Termination of pregnancy is legally allowed in the Netherlands if performed in accordance with the Termination of Pregnancy Act (Wet afbreking zwangerschap), and no later than the gestational age beyond which, according to professional judgement, a newborn can be expected to independently survive outside the uterus. At present, this is set at 23 weeks and 6 days of gestation. Beyond this limit, a 'late termination' is legally allowed only in two narrowly circumscribed categories: 1. conditions with a diagnosis that make it reasonable to expect that the newborn cannot survive outside the uterus[18]; 2. conditions with a diagnosis that render it beyond reasonable doubt that,

[17] The difficulty with establishing more evidence, is that practice has moved far beyond the point where proving suspected benefits with new trials would still be considered acceptable by an ethics research committee.
[18] NVOG. Commissie Late Zwangerschapsafbreking Categorie 1 (LZA1). https://www.nvog.nl/themas/kwaliteit/commissies/commissie-late-zwangerschapsafbreking-categorie-1-lza1/

postnatally, doctors will refrain from medical treatment[19]. Examples of the first category are anencephaly of renal agenesis; of the second, severe spina bifida or progressive hydrocephalus.[42]

A timely prenatal diagnosis, either with an eye to enabling a timely intervention or in view of the termination limit, is not only a matter of (improving) test quality, but also of the stage of development of the relevant organ systems. In this respect, the timing of the present STAS between weeks 18+0 and 21+0 is a compromise: optimizing the yield of serious abnormalities while still allowing time for a final diagnosis prior to the legal termination limit.[15] As this is a comprise, it does occur regularly that far-reaching decisions have to be made under time pressure (in cases where a late termination is not an option). In fact, with advancing technology, diagnostic follow up testing has become more and more time consuming, leading to an increasing number of cases with a prenatal diagnosis after the legal termination limit.

3.2 Harms of prenatal ultrasound screening

As goes for all forms of medical screening, prenatal ultrasound also comes with possible harms for those undergoing the test. These mainly take the form of an adverse effect on psychological wellbeing (e.g. distress, anxiety, depression) in pregnant women who are confronted with abnormal findings.[43-45] For those with a normal outcome, participation in the screening is generally reassuring – although after a temporary increased state anxiety prior to the scan.[46] However, the message that no abnormalities were found can also lead to false reassurance.[45]

In a large prospective Norwegian study, “advanced gestational age at diagnosis, the severity of the anomaly and significant prognostic ambiguity” were singled out as the strongest predictors of high levels of distress.[47] In line with other studies, the same group found that after confirmatory diagnosis, levels of distress again decline to an almost normal level, “but with persistent symptoms of depression towards the end of pregnancy”.[48]

Where a finding of a fetal abnormality is confirmed, pregnant women and their partners need to make decisions about further pregnancy management, often including the choice about whether to continue or terminate the pregnancy. While this is a difficult decision in itself, it is even more difficult where the diagnosis and/or prognosis are (initially) unclear.[49] Earlier detection provides women or couples with more time for both diagnostic testing and careful decision making. In the literature, attachment theory is seen as explaining why gestational age is a strong predictor of termination decisions, with women being less likely to terminate a more advanced pregnancy, next to the

[19] Regeling beoordelingscommissie late zwangerschapsafbreking en levensbeëindiging bij pasgeborenen en kinderen 1-12 jaar. https://wetten.overheid.nl/BWBR0037570/2024-02-01

perceived seriousness of the condition.[43, 50] It has also been reported that an earlier gestational age at termination comes with lower levels of long-term psychological consequences.[51-53]

Abnormal findings that turn out to have been false positives, lead to distress that in hindsight was unnecessary; false positives may also lead to iatrogenic harm in cases where invasive procedures that come with a (small) miscarriage risk are needed to make a final diagnosis.[54]

4. Benefits and harms of adding FTAS to the prenatal screening program

As it is unlikely that FTAS can detect structural anomalies that are not observed with STAS, adding FTAS to the present prenatal screening program with STAS is not expected to lead to a higher total yield of abnormalities diagnosed prior to 24 weeks (i.e. legal termination limit). An exception to this are genetic abnormalities diagnosed after referrals for enlarged NT as part of the FTAS-protocol. Depending on whether these can be found with NIPT, or come with structural abnormalities visible with STAS, many will otherwise only be found after birth.[55]

The main expected benefit of adding FTAS is not better, but earlier diagnosis of major structural anomalies [56] allowing women (and their partners) more time for reproductive decision-making, including earlier termination of pregnancy which may have less psychological impact compared to late pregnancy termination.[1, 57] The major anomalies that may be found with FTAS consist of two groups. The first is referred to as FTMA: First-Trimester Major Anomalies. These are "severe structural anomalies that can be expected to be 'always' detected by FTAS"[20], such as anencephaly. The second group consists of major anomalies that can "often be detected" on a first-trimester scan, such as spina bifida. Finally, a potential benefit of FTAS is the detection of conditions that require interventions and/or adapted obstetric care already early in pregnancy.

The potential harm of FTAS comes with the degree to which this extra screening test would add to the psychological burden for pregnant women (and their partners). Specific concerns relate to referrals for findings that turn out to be false positives, or where early referral leads to a longer period of uncertainty about the final diagnosis, as compared to finding the relevant conditions with STAS. As always, debates about prenatal screening for fetal abnormalities touch on the ethics of abortion. Here, a possible concern is that first-trimester ultrasound would come with a lower threshold for termination of pregnancy, also for less severe abnormalities.

4.1 IMITAS results

The IMITAS study [1] shows that FTAS, when offered between 12+3 and 14+3 weeks of gestation and performed by trained ultrasonographers on the basis of a uniform referral protocol, has a high sensitivity of 84.6% for FTMA. The sensitivity for all anomalies combined was much lower at 31.6%, while in line with earlier reports in the literature.

[20] On the basis of the literature and expert judgement.[1]

The referral rate was 1.0%[21], of which 40.9% (537/1312) were true positives[22], including 332 structural anomalies (mainly multiple congenital anomalies and heart defects), 117 genetic (almost half of which trisomy 21), and 82 'other' (mainly sonomarkers and abnormal biometry, but also placental/umbilical cord anomalies and amniotic fluid anomalies).

There were 231 referrals for increased NT, leading to 17 structural, 45 genetic and 17 'other' anomalies confirmed at the first diagnostic scan. Of the genetic anomalies found after NT referral, most were chromosome abnormalities, including trisomies that could have been picked up by NIPT, had that test been done prior to FTAS.[23] But there were also 4 severe genetic disorders, each leading to a termination, that could not have been found with NIPT, and that might have been missed with STAS since the increased NT usually has resolved, or is resolving, by 14 weeks.[24]

The median moment of final diagnosis for referred cases, defined as "the date (…) at which sufficient knowledge on the prenatal diagnosis and prognosis was available to parents for reproductive decision-making", was at 16+1 weeks of gestation. The median time to diagnosis was 9 days for FTMA, 17 days for genetic anomalies, and 20 days for all structural anomalies. The percentage of cases with a diagnosis before 18 weeks of gestational age was 81.7% (n=103) for FTMA, 81.2% (n=95) for genetic anomalies, and 56.6% (n=188) for all structural anomalies.[2] In 50.1% of all cases with a confirmed abnormality, the pregnancy was terminated.[25]

The larger part (59.1%) of referred cases (775/1312) were 'false positives'[26], including 586 anomalies that were not confirmed at the first detailed diagnostic scan[27] and 189 that were confirmed at the first scan, but resolved in the second-trimester ('transient findings').[28] Of the 127,979 women with a normal (or incomplete) FTAS result, 1164 had an anomaly detected with STAS.[29] These 'false negatives' were mainly structural anomalies (n=1076), including heart defects (n= 268) and urogenital anomalies (n=262).

[21] For STAS, this was 4% in 2022: https://www.vzinfo.nl/bevolkingsonderzoek/20wekenecho
[22] As confirmed at final diagnosis <24 weeks. There were 721 abnormal findings at the detailed diagnostic scan after referral. This includes 189 transient findings. Note that in the IMITAS study reports that we here summarize, terms used to describe general test characteristics ('positives', 'false-positives', 'false-negatives'), refer to FTAS as a test for all types of anomalies, rather than only for major anomalies.
[23] Not all women who decide to have FTAS also accept NIPT screening for chromosome abnormalities.
[24] For this paragraph unpublished data were used from the IMITAS document: "Nuchal translucency in the era of NIPT: the diagnostic yield".
[25] In 49.4% of pregnancies with a structural anomaly, in 82.9% of pregnancies with a genetic anomaly, and in 6.1% of pregnancies with a confirmed 'other' finding.[2]
[26] FPR 0.8% (775/98,830). See also footnote 22.
[27] Of those not confirmed, the majority were referred because of abnormal fetal biometry (n=251) and structural anomaly (n=226).
[28] Transient findings comprised referrals for increased NT (n=52), abnormal biometry (n= 47) and distended jugular sacs (n=17). In nine cases with transient findings, anomalies were present after birth.
[29] FNR 68.4% (1164/1701). See also footnote 22.

Taken together, these data confirm that, as compared to screening with STAS only, FTAS enables a significantly earlier diagnosis, leading to more time for reproductive decision-making and earlier termination of pregnancy. This suggests that FTAS meets important expectations concerning its main potential benefits. However, the IMITAS data also show that the scan leads to a significant number of false positives, many of which are found to be false alarm only in the course of the second-trimester. A significant percentage of those referred for a suspected fetal anomaly at FTAS, face a lengthy diagnostic trajectory, with uncertainty lasting up to 18 weeks of gestation and longer.

For some women and children, FTAS may also come with preventative benefits. This happens when a condition is found whose prognosis can be considerably improved through an effective intervention available already early in pregnancy. An example of such a diagnosis found in the IMITAS study, was a TRAP-sequence[30], where timely treatment led to survival of the 'pump twin'. However, such cases are very rare. With STAS, there are far more instances of diagnoses enabling a wider range of timely interventions, including induction of labor, or birth in a specialized center.

4.2 Women's views and experiences

In order to be able to prospectively assess the effects of adding FTAS to the prenatal screening program on women's wellbeing and experiences, surveys were held at different time points during pregnancy and postpartum, among women in both the 'BEFORE' and 'AFTER' cohorts[31], plus in-depth interviews among women in both cohorts who chose to have their pregnancies terminated because of a fetal abnormality.[32] Surveys are useful as large amounts of information can be uniformly analysed with validated measures; however one should be aware that they come with limitations. Generally, participation tends to be lower among those with lower socioeconomic status, health literacy, etc. Moreover, in the already emotionally charged setting of pregnancy, women at higher stress levels may find certain questions too confronting to properly respond to.

On the basis of the surveys, an exploration of women's motivations for having or not-having FTAS (AFTER cohort) led to very similar reasons as found in other studies of reasons for (non-)participation in prenatal screening for fetal abnormalities: to be reassured, to want to know that everything is all right with the pregnancy and one's future child. Of those deciding not to have FTAS,

[30] Twin reversed arterial perfusion (TRAP) sequence occurs in 1% of monochorionic twin pregnancies. The blood systems of the twins are connected, with one twin ('acardiac') not properly developed and the other ('pump twin') having a low chance of survival, if left untreated. Treatment consists of selective termination of the acardiac twin. When missed at the dating scan (where the condition may be mistaken for a miscarriage of half of a twin pregnancy), these conditions will often be found too late with STAS.

[31] See section 1.2.

[32] 14 interviews were held in the BEFORE cohort, with terminations of pregnancy following an abnormal STAS, between 20+4-23+6 weeks of gestation; 37 interviews were held in the AFTER cohort, with terminations following an abnormal FTAS, between 13+6-23+6 weeks of gestation. In the AFTER cohort, 23/37 interviews were held with women who had a termination prior to 18 weeks of gestation, 3/37 with women who had a termination at ≥20 weeks, and 11/37 with women who had a termination after an abnormal STAS, following a normal FTAS.

17.4% (n=83) said they would already have screening with STAS. A smaller percentage (6.7%; n=32) indicated that, according to them, an early scan was unreliable. Part of these responses may reflect the context, in which FTAS was explicitly offered in a research setting rather than an established screening test.[2]

Satisfaction was measured using a validated scale for decision-regret, showing overall low regret scores regarding participation, below the threshold for clinical relevance, also in the group of women having received an abnormal FTAS result. In the comparison between having an early versus late scan with abnormal results, higher mean scores of decision regret were found in the FTAS-group, although still below the threshold of clinically relevant symptoms. Most women whose normal FTAS result turned out to have been false negative had little regret of participating. Still, in this group, 15.3% (n=67) were found to have moderate to severe regret at 24 weeks, increasing to 17.1% (n=75) postpartum.[2]

The surveys further explored the psychological impact (distress, anxiety, depression) of having FTAS versus STAS, both with normal and abnormal (including false-positive) results. These comparisons show very similar and generally reassuring scores, including patterns over time, on relevant scales for measuring these effects.[2, 4] In the comparison between having an early versus late scan with normal results, a noteworthy finding is a clinically relevant higher anxiety at 15 weeks of gestation in the FTAS-group, as it does not show an immediate reassuring effect of the scan, as one might have expected. A further comparison between the two cohorts looked at the psychological impact of having an adverse STAS-finding after a normal FTAS result (false negative), as compared to having had no screening with FTAS, and found no significant differences on relevant scales.[2]

Finally, the two cohorts were used to compare the experiences of women having an early (<18 weeks of gestation = after FTAS-referral) versus late (≥20 weeks = after STAS-referral) termination of pregnancy. The median gestational age at termination among women included in this survey was 15+2 versus 22+2 weeks of gestation. In the early termination group, this was relatively more often for a chromosomal abnormality (40.9% n= 61) than in the late termination group (17.6% n= 6). There were no significantly relevant differences on the scales for anxiety and decision regret. Whereas decision regret scores (with regard to having had either FTAS or STAS) were low in both groups, the majority in both groups had clinically relevant anxiety scores. On three further relevant measures: impact of event (assessing distress), grief, and depression, women in the early termination group had significantly lower scores than those with a late termination. For impact of event, the difference remained over time while scores decreased from 2 to 6 months postpartum; for grief and depression, scores were no longer different at 6 months. Two months postpartum, women in both groups were asked whether they had experienced any time-pressure with regard to decision-making

about whether or not to terminate the pregnancy. Whereas in the late termination group, 38.3% of women had wanted more time for decision-making, this was only 2.7% in the early termination group.[2]

In addition to surveys, interviews are important, as they invite respondents to share detailed, open-ended experiences, thus offering deeper insights to researchers. In both cohorts, interviews were held with women who chose termination. These also included experiences of women in the AFTER cohort who had a late termination following an early referral, as a consequence of a prolonged diagnostic trajectory. For instance, one woman whose pregnancy was eventually terminated at 22+2 weeks of gestation, reported to have remained in uncertainty since the scan at 13 weeks. She found that this had taken way too long. Several respondents in both cohorts said that they had not experienced the termination decision as difficult in itself, although it was certainly a hard one for them to make. This was explained with reference to the severity of the diagnosis. In line with this, another respondent said that for her, uncertainty about the severity of the diagnosis was what had made her choice difficult, and yet another that to be able to make this decision, it had been important to have a definite diagnosis. While the interviews confirm time-pressure as an issue only for those with a late termination (≥20 weeks of gestation), some women in the BEFORE cohort also indicated that the pressure of time meant that a decision could not be postponed. Although early versus late termination did play a role in the experience of bonding and parental identity, there was also much variety in this respect among the interviewees. With respect to the period postpartum, many women in both cohorts reported living with the impact of what had happened, not just those who had a late termination. However, a large part of the interviewees in the AFTER cohort said they had been able to incorporate the experience in their lives and had somehow been able to move on.

Together, the findings from the surveys and interviews indicate that while adding FTAS to the prenatal screening strategy does not have a large adverse effect on the psychological burden of prenatal screening for most women, the psychological impact of an early termination of pregnancy is lower than that of a late one. Given that women report positive experiences with having more time for decision making, this seems to confirm the value of having FTAS added to the prenatal screening program.

These results of the IMITAS study are in line with the findings of an earlier cohort study of women offered a fetal anomaly scan at 13 weeks in the North of the Netherlands.[57] One of the conclusions of that study was that the reassuring absence of a lasting adverse effect also applied to those confronted with a false-positive test result.[33] Unfortunately, specific data are missing with respect

[33] As stated by the authors: “Even though we found a temporary increase in anxiety levels and decrease in well-being following false-positive results at the early scan, these normalized again in the course of pregnancy indicating no long-term detrimental effect on maternal anxiety and well-being.”[57]

to this group in the reports from the IMITAS study. Given that for these women, especially for those who had an initially confirmed abnormal result that later turned out to be false-positive, the harms of participation may well have exceeded the benefits, it would have been important to reconfirm those reassuring findings. Using the data of the IMITAS surveys, it should still be possible to conduct a sub-analysis of their views and experiences. We propose to also do so with respect to those confronted with a lengthy diagnostic trajectory due to uncertainty. Additionally, it would have been important to interview women from these groups, which was not foreseen in the IMITAS study.

4.3 Accounting for other first-trimester scans

While interim conclusions sound favorable, it should be noted that in the present situation pregnant women are already offered first-trimester scans other than FTAS, and that these do lead to referrals for suspected fetal abnormalities, even without being designed or operated for that purpose.[34] Most notably, this includes a routine dating scan measuring crown-rump length at around 10-12+6 weeks gestation that all pregnant women in the Netherlands do in fact undergo.[35] When the effects of those other scans are taken into account, the added value of FTAS to the current screening program seem less obvious.

This was shown in a comparison of a one year yield[36] of detected anomalies as a result of referrals from routine scans prior to 18 weeks in the BEFORE cohort (=without FTAS), and the calculated yield of a 'fictive AFTER' cohort in which both routine scans and FTAS are offered. For this fictive AFTER cohort, data from the BEFORE cohort (referrals < 12+3) were combined with the AFTER cohort. This strategy was chosen because the AFTER cohort itself only contains data on referrals from FTAS, without regard of the effects of other first-trimester scans.

Although these calculations led to a much higher number of referrals in the fictive AFTER than in the BEFORE cohort, this did not translate in a comparably higher percentage of diagnosed major anomalies. In fact, both the number and proportion of FTMA was lower in the dataset of the fictive AFTER cohort than in that of the BEFORE cohort, whereas for the category "often detectable" major anomalies (such as spina bifida), figures were higher in the fictive AFTER dataset. A further effect of adding FTAS was more false-positives, uncertain findings and detection of non-major anomalies as compared to the situation in which only other routine scans were offered.[3]

[34] Including referrals because of enlarged NT – large enough to be seen by eyeballing, without the need for measuring.
[35] NVOG. Protocol Datering van de zwangerschap. Versie 2.0, 2018. Datering-van-de-zwangerschap-2.0-update-aug-2018.pdf (nvog.nl) Further scans that women receive prior to 18 weeks of gestation include an obstetric viability scan (before 8 weeks), commercial scans performed for non-medical reasons including sex-determination (around 15-16 weeks), as well as scans for pregnancy complications or as part of obstetric check-ups.
[36] Extrapolated for the purpose of this comparison from 8 months to one year.

For other main outcomes: time to diagnosis and gestational age at termination, data from the BEFORE cohort (=referrals from routine scans without FTAS) were compared with those from the AFTER cohort (referrals from FTAS). For FTMA, the time to diagnosis was comparable in both cohorts at 8-9 days, but the gestational age for all anomalies at termination was significantly earlier in the BEFORE cohort (13+5 versus 15+3 weeks). For all anomalies, proportionally more pregnancies resulted in termination or intra uterine fetal demise (IUFD) in the BEFORE cohort, with a significant earlier gestational age at birth. Lastly, false-positive referrals were less in the BEFORE cohort (34% versus 44.6%), as were transient findings (18.8 versus 26%).[3]

In light of these outcomes, it is clear that an evaluation of the benefits-to-harms ratio of introducing FTAS in the prenatal screening program cannot ignore the impact that other first-trimester scans such as the dating scan already have on the number, nature and timing of prenatal diagnoses. Detection rates could not be calculated for these routine scans and definite comparisons can therefore not be made. However, indications are that, against this background, the benefits of FTAS in terms of added yield of major anomalies in early pregnancy is mainly in the category of 'often detectable' anomalies, as other first-trimester scans are quite good at finding FTMA. This added value of FTAS comes at the price of a higher gestational age at termination for all anomalies, as well as higher proportions of false positives (including transient findings), non-major anomalies and findings with an uncertain diagnosis or prognosis.[3]

5. Voluntary participation based on informed choice

Women were offered FTAS as part of the IMITAS study, during a prenatal counselling session in which all pregnant women are also informed about other tests in the prenatal screening program for fetal abnormalities (NIPT and STAS).

In the IMITAS study, 74.9% of women chose to have FTAS. The uptake figures for 2022 for NIPT, FTAS and STAS were 57.8%, 75.5% and 85.6%, respectively.[37] The uptake for STAS has remained stable since 2021, meaning that, so far, it has not been influenced by the introduction of FTAS. The uptake of FTAS may further increase should the scan no longer be offered in the context of research, but as a regular part of the screening program.

Apart from the co-payment for NIPT that was only recently discontinued[38], the higher uptake of ultrasound screening as compared to screening for chromosome abnormalities seems to reflect the fact that, for many women, prenatal ultrasound is more than just a further screening test.[12] It is also an opportunity to 'see the baby', with a proven positive effect on maternal-fetal bonding.[58] At the same time, there is a concern that precisely because of the broader array of reasons behind the generally positive attitude of pregnant women regarding prenatal ultrasound, they may insufficiently be aware of its screening character and the possible consequences of a non-reassuring result.[59, 60] A further concern is that because of the wide range of abnormalities (targeted or non-targeted) that can be found with ultrasound[39], pretest information and counselling is necessarily general, and that as a consequence, women (or couples) can only in general terms be prepared for the decisional challenges that they may face in the wake of an abnormal finding of the scan.[61]

What makes a decision informed, is not just that it is based on adequate (i.e. 'decision relevant') knowledge, but also that it is consistent with the decisionmakers' values and is the result of deliberation.[62, 63] In the surveys held among participating and non-participating women in the IMITAS study, these aspects were explored using knowledge questions drawn up by a multidisciplinary expert group and validated measures for deliberation and decisional conflict. In terms of these instruments, it was found that almost 90% in both groups had adequate knowledge of FTAS as a screening test for fetal anomalies and also that around 70% had made their decision on

[37] RIVM, Pre- en neonatale screeningen (PNS). Monitor 2022 screeningsprogramma de NIPT en het SEO. https://www.pns.nl/documenten/monitor-2022-screeningsprogramma-nipt-en-seo.
[38] 2022 was the last full year in which women still had to pay 175 euros for NIPT.
[39] Until recently, there was a clear difference in this respect between ultrasound screening for structural anomalies and screening for three common trisomies (trisomy 21, 18, and 13), about the nature and prognosis of which women had to be informed prior to deciding about having the test. This distinction is rapidly becoming something of the past with the tendency towards broadening NIPT-based screening, which in the Netherlands will now also include large structural chromosome abnormalities.

the basis of deliberation.[40] Decisional conflict scores were low in both groups, but significantly lower among women who chose not to have FTAS as compared to those who did. Finally, it was found that over 99% in both groups did not perceive pressure from anyone (partner, professional) to accept or decline the offer of screening with FTAS. On the basis of these results it was concluded that, in the IMITAS study, women were enabled to make a voluntary and informed decision about participation.[41]

It is important to note that this refers to decision-making about a testing offer in what was explicitly presented to pregnant women as a research context, with participation involving a written consent. Should FTAS be introduced as a regular part of the screening program, women may be more inclined to see the test as a routine element of obstetric care in pregnancy, which may then also influence the degree to which, in terms of these concepts and scales, decision-making is indeed informed.[42] Moreover, the reassuring outcome of the relevant surveys does not take away the concern about the inevitably generalized nature of what counts as adequate pretest information. Finally, as is the case with many studies, surveys involve higher-educated women and may introduce recall and selection bias.

In the context of prenatal screening for fetal abnormalities, the emphasis on informed decision-making goes beyond the general principle that, both in health care and public health, people should not be pressured to undergo procedures against their will. In this context, a further argument is what we have earlier (section 2.2) referred to as the 'autonomy aim' of prenatal screening for conditions where a positive diagnosis provides women with no other options but a choice between terminating the pregnancy or preparing for a child with special needs. While the Dutch prenatal screening program reflects a high awareness of the importance of this atypical screening aim, this remains an issue for continuous vigilance, also when introducing a new screening test.

For example, a realistic concern is that women who have decided not to have NIPT-screening because they would never terminate a pregnancy for Down syndrome, are confronted with precisely that diagnosis as a result of FTAS. This is not entirely new, as trisomy 21 may also be found with STAS, but the inclusion of NT as a sonomarker in the FTAS protocol significantly increases the odds.[43] For these women, the fact that they are now confronted with the choice they earlier wanted to avoid, can either be seen as a problematic instance of what has been called the screening trap [65],

[40] Unpublished data from IMITAS document "Methods and results of informed choice."
[41] Because attitude questions were missing, Informed Choice could not be measured in accordance with the multidimensional measure of informed choice (MMIC)
[42] For STAS, a recent paper by the IMITAS study group found that 54.8% made an informed choice, 89.6% had good knowledge, 59.8% had deliberated their choice.[60] For NIPT, 75.5% was found to make an informed choice.[64]
[43] In the IMITAS study (AFTER cohort), researchers found 57 cases of aneuploidy. In the majority of cases the parents didn't opt for the NIPT, but these cases did show high (termination) rates.[3]

or indeed as an opportunity for them to reconsider that earlier decision. In order to help pregnant women manage their expectations, it is important that counselors discuss the possible consequences of this overlap between NIPT and FTAS as part of pretest information and counseling.

6. Quality of screening method and screening process

The IMITAS study shows that FTAS has a high sensitivity for FTMA (84.6%). In light of the use of a uniform extended referral protocol and specifically trained ultrasonographers, this may well be in the region of the higher limit of what can be achieved in a national screening program.[1, 3] Sensitivity is much lower for all anomalies combined (31.6%) and the test comes with an overall positive predictive value (PPV) of only 40.9%, meaning that for 6 in 10 women with a suspected fetal anomaly at FTAS, this turned out to be false alarm. While more specific information on test characteristics (e.g. for major anomalies that are 'often detectable' and for non-major anomalies) would have been relevant for this evaluation, those data are not available. It is important to note that this is also the case with respect to STAS.

6.1 Screening method

To make sense of these results, an important question is whether FTAS is to be seen as a test for FTMA, for major anomalies, or for any anomalies that a first-trimester scan can reveal. Some may argue for the latter view, in light of the fact that many pregnant women want to be informed about everything that the scan can reveal about the health of their future child, however uncertain or inconsequential. As indicated in the above discussion (section 2.2), this is difficult to reconcile with the notion of screening as a public health service. As such, FTAS can only be justified if it leads to the diagnosis of conditions that may either enable women (or couples) to make meaningful reproductive choices, or allow interventions that significantly improve the odds of a healthy outcome of the pregnancy (section 2.1).

While these considerations favor the view of FTAS as a test for all major anomalies (structural, genetic and 'other') that can be found in the first-trimester (rather than only for FTMA), they also mean that a low detection rate for 'all anomalies combined' should not be considered a problem. This is relevant for the Health Council's suggestion to adapt the FTAS referral protocol in order to improve the benefits-to-harms ratio of the screening. As explained earlier (section 1.2), the meant protocol was drawn up specifically for the IMITAS study. It uniformly specifies the biometric and anatomic assessments and measurements on the basis of which the ultrasonographer must decide about referrals for suspected fetal anomalies. The referral protocol was designed as a quality standard to maximize the overall yield of abnormalities that can be found with FTAS. While this was certainly useful in the context of the study, it is not obvious that the same protocol should remain in place when introducing FTAS in the regular screening program. For instance, one might decide to refrain from specific biometric measurements or sonomarkers that contribute less to the early detection of major anomalies than to the amount of problematic 'noise', in terms of false positives and inconsequential or uncertain findings. This re-evaluation should be performed by a team of

tertiary care specialists with expertise in post-test referrals and with knowledge of relevant international standards.[66]

An ongoing debate in this connection concerns NT, as apart from contributing to such 'noise', NT referrals may lead to finding some severe genetic disorders that will not be brought to light by NIPT and may also be missed by STAS. To improve the balance between these possible outcomes one may perhaps consider easing the measurement requirements for NT, as even with eyeballing, without upfront measuring according to protocol, a greatly enlarged NT will still be seen and thus be referred by the ultrasonographer. As shown in the analysis of the BEFORE cohort, this is also the case where other first-trimester scans are concerned, with almost 40% of all referrals done for NT.

At the same time, the IMITAS results suggest that there may be scope for improving the FTAS-protocol (and related training of ultrasonographers) not just with an eye to 'noise reduction', but also with regard to increasing the detection of major anomalies with FTAS, especially in 'often detectable' category.[44] This point was made in a recent conference presentation of the study results by IMITAS researchers prof.dr. Monique Haak and prof.dr. Mireille Bekker. They suggested that of the 1076 major structural anomalies that were missed in the IMITAS study, a considerable part ("perhaps 146") should be detectable in the first-trimester.[45]

Apart from a recalibration of the FTAS protocol, improvement of the benefits-to harms ratio of this new screening test may also be expected of a further learning curve of professionals involved in confirmatory diagnostic testing after FTAS referrals. The greater their uncertainty with regard to diagnosis and prognosis, the longer the diagnostic trajectories for women, including for those with false-positive findings.

The IMITAS-study policy to not refer incomplete scans, contributes to the relatively large number of false-negative findings. While it seems too early to reconsider this policy, we recommend efforts aimed at improving the level of assessments so as to bring down the number of scans that are unnecessarily listed as incomplete. We also recommend a planned evaluation in due time of the non-referral policy, with an eye to optimizing the balance of false positives and negatives.

Finally, the discussion about target conditions and protocol has implications for screening with STAS as well. As observed in the introduction, STAS was until recently licensed as a screening test for neural-tube defects, more specifically spina bifida. While this was clearly too narrow, it does not

[44] In the IMITAS-survey among professionals, some specific proposals were made, for instance with an eye to improving the detection of major cardiac anomalies.

[45] This might apply to 27 of the 268 heart defects not found with FTAS, 26/30 spina bifidas, 13/54 Multiple Congenital Anomalies (MCA), and 56/80 genetic disorders. Monique Haak & Mireille Bekker, 'Small things matter', presentation at the Gynaecongres conference of the Dutch Association of Obstetrics & Gynecology (NVOG), Houten, 15 November 2024.

follow that STAS should instead be offered as a test for any possible anomalies. If that is problematic for FTAS, the same goes for STAS.

6.2 Screening process

General conditions for securing the quality of screening with FTAS can expectedly be fulfilled when this new test is incorporated in the existing screening program with its centralized set-up, monitoring system and mandatory training programs.

It is important that FTAS optimally fits in with the prenatal screening trajectory as a whole. A relevant aspect is that in the latter part of the first-trimester, pregnant women already have several obstetric consultations and tests. The high acceptance of the FTAS offer suggests that women do not regard this further test as too much of a burden. When asked at 15 weeks, a third of those in the BEFORE cohort indicated they would have wanted to be offered a scan during that stage of pregnancy.

A specific point of attention is the overlapping relation with NIPT, given that chromosome abnormalities for which NIPT is offered as a screening test, can also be found with FTAS, either as a result of NT-measurement, or because structural anomalies seen on the scan are often part of a syndrome. If FTAS is offered between 12+3 and 14+3 weeks of gestation, NIPT will in most cases already have been done. Still, professionals must be aware that this need not always be the case, and also that part of the women who decline NIPT may well decide to have FTAS, which may then lead to situations as discussed in section 5.

For decisions about whether and how to formally introduce FTAS, an important issue concerns the implications of the fact that many of the anomalies screened for with FTAS, are already detected as a result of present routine scans, most notably the dating scan at 10-12+6 weeks of gestation. As a consequence, adding FTAS not just means adding this as a further scan to the present screening program with NIPT and STAS; it means: adding it to the present situation in which apart from those screening tests, women are also having other scans that lead to referrals and diagnoses.

First, it can be asked what this entails for the dating scan. As the dating scan is considered a purely obstetric instrument, separate from screening, women are usually not informed that having a dating scan may lead to referrals for fetal abnormalities and into a trajectory of further testing. From an ethical point of view, it can certainly be argued that they should be better prepared for this than is currently the case. However, this may not be easy to achieve precisely because of the delineation between care and screening.

Second: what does it mean for the possible role of FTAS that major anomalies are also found with other first-trimester scans? Here we comment on three possible scenarios.

Scenario 1: Screening without FTAS

This scenario involves refraining from introducing FTAS in the screening program. In practice, it means stopping with FTAS, which is currently offered on the basis of an extension of the research license for the IMITAS study, pending a decision about its possible formal introduction as a screening test for major anomalies in early pregnancy. Apart from a possible financial argument (see section 7), one argument for refraining from introducing FTAS might be that *de facto*, part of the benefits of early detection (especially FTMA) are already obtained with routine scans such as the dating scan (see section 4.3).

While it may seem that the 'Screening without FTAS' scenario amounts to keeping things as they were prior to the start of the IMITAS study, this ignores the difference between simply not having a first-trimester ultrasound screening scan, and relying for this part of the screening program on referrals resulting from additional findings of other first-trimester scans. If the latter is what the 'Screening without FTAS'-scenario is about, it amounts to regarding those other scans (e.g. dating scan) as informal screening tests for fetal abnormalities. This is inherently problematic, precisely because those scans are offered for another purpose than screening for fetal abnormalities and operated by ultrasonographers not trained to do screening scans. As referrals from such scans consist of abnormalities that those operators happen to see when observing the fetal image for different reasons, they cannot be integrated in a quality controlled screening program. Nor can requirements be met for proper pre- and post-test information and counselling with regard to such findings. Where scans are not meant to find fetal abnormalities, women cannot be adequately prepared for such findings, which is at odds with the autonomy aim of prenatal screening for fetal abnormalities.

Scenario 2: Screening with a combined First-Trimester Anomaly & Dating Scan

In a second scenario, FTAS is combined with the dating scan, leading to an early ultrasound screening test at 10-12+6 weeks, for which ultrasonographers currently doing the dating scan will require additional training. For this, an adapted referral protocol will need to be drawn up, that takes account of the earlier gestational age at which this combined scan will be performed.[46] The dating scan as a separate obstetric procedure will cease to exist, as in this scenario, it will be incorporated in FTAS. For pregnant women, this scenario avoids the burden of a further testing moment, while still giving them part of the benefits of FTAS, notably early detection of FTMA, at a low rate of 'noise'. However, major anomalies in the 'often detectable'

[46] NT testing is recommended from 11 weeks of gestation, thus making a problematic fit with this proposal.

category will less often be found as a result of earlier testing, rendering this scenario suboptimal as a screening test for all major anomalies. [56]

Moreover, from an ethical point of view, a problem with this scenario is precisely the combination of scans that are performed for different purposes. While it should still be possible for women to make a well informed choice to have a dating scan while declining the screening offer[47], a standard incorporation of the former into the latter sends the message that having both is what pregnant women are expected to do. This links in with concerns about 'routinization' in the debate about the ethics of prenatal screening. [67]

Scenario 3: Screening with added FTAS

A third scenario entails formally adding FTAS (at 12+3-14+3 weeks of gestation, possibly with an adapted referral protocol), to the program of prenatal screening for fetal abnormalities. In addition to the problems and limitations of the first two scenarios, the main argument for this scenario are the clear benefits for pregnant women of a screening program in which major anomalies (not just FTMA) are diagnosed at an earlier stage than is possible with STAS. This argument presupposes that the harms coming with false positives, uncertain findings, or detected anomalies outside the target range, do not outweigh those benefits.

It has been suggested that with FTAS in place, STAS might be "revisited to include a detailed re-examination of only organs, such as brain and heart, that are still developing or can be better visualized later in pregnancy"[16] However, the IMITAS results suggest that it would be too early to take such a step as long as many major anomalies are still missed with FTAS and a significant percentage of FTAS results are shown to be false positives with STAS.

[47] As stated, a well-informed choice in the matter would require knowing that the dating scan may lead to suspicion of fetal anomalies.

7. Cost-effectiveness and justice

Whether the costs of adding FTAS to the prenatal screening program can be justified is a matter of just allocation of scarce financial resources. In this connection, an important difference with the existing screening using NIPT or STAS is that those tests may well lead to a reduction of the costs of care for those living with the relevant conditions.[68] While sensitive, there is nothing inherently problematic about this 'savings argument', as long as it is not turned into an alternative account of the aim of prenatal screening.[69, 70] However, it certainly does not apply to FTAS, as this new screening test would lead to finding anomalies earlier, rather than finding more of them.[48] This means that even with a positive benefits-to-harms ratio, it remains an open question whether those benefits outweigh the higher opportunity costs of adding FTAS to the screening program, both financially and in terms of mobilizing scarce health personnel and other resources. A further health-economic study, based on costs per case detected, (not part of IMITAS) will be needed to inform this assessment (eventually a political decision), either in favor of adding FTAS or against doing so.

Should FTAS be implemented, this may be done either with or without co-payment from pregnant women. At present, both NIPT nor STAS are offered free of charge, but whereas this has always been the case with STAS, co-payment for NIPT has only recently (1 April 2023) been skipped. Arguments for co-payment may be economical: to reduce the cost of the program, or ethical: signaling the fact that although the test is offered in the context of care, having it should not be regarded a matter of course, but be the result of personal deliberation.[71] For this latter purpose a small co-payment would suffice.

One of the arguments brought forward against co-payment is that it would be unjust to ask pregnant women to contribute to tests that actually save the public money.[70] While this may apply to NIPT and STAS, it clearly does not to FTAS, for reasons already stated: as an extra test without extra yield, FTAS comes with higher costs for the tax payer. However, other arguments against co-payment apply to all forms of prenatal screening, including FTAS. We agree with Bunnik et al. that co-payment is not necessary to send a message about the importance of deliberation, as this can also and even better be achieved through proper pre-test information and counselling. If it comes to moral messages, co-payment may even have the counterproductive effect of telling pregnant women that participation in screening is not that important for them. Finally, and most importantly, co-payment raises a financial barrier that for some women will inevitably be higher than for others, thus leading to a morally problematic inequity of access.[72]

[48] Except perhaps for a small number of severe genetic disorders found as a result of NT-referrals after FTAS (part of which may also be found through the dating scan).

8. Wider ethical debate

In this section, we briefly discuss how FTAS relates to wider debates, first about the acceptability of abortion, as seen from the perspective of the moral status of the fetus, and second about the acceptability of selective abortion, as seen from the perspective of the 'disability rights critique'.

8.1 Moral acceptability of abortion

Those holding that the fetus at any stage of pregnancy, or even the embryo as from conception, is a human person with the same right to protection that all human persons have, will find that termination of pregnancy is always morally unacceptable.[73] Clearly, this is not the view on which the Dutch Termination of Pregnancy Act is based, nor can it be reconciled with the existence of a prenatal screening program for fetal anomalies whose prenatal detection only allows for a choice between 'preparation or termination'. In its 2001 report on Prenatal Screening, the Health Council justified offering such screening with reference to "a broadly shared consensus", according to which the fetus has a "relative and increasing" moral status. While this gives it a claim to protection, the relative nature of this status entails that situations may occur in which the weight of other considerations prevails.[12] The legislator speaks of the "emergency situation" of the woman that makes termination inevitable, leaving it to her to determine whether her situation (*in casu*: being confronted with the diagnosis of a fetal anomaly) would fit that description. The time limit for this ('viability'; *de facto* 24 weeks of gestation), can be read as the legal turning point where the increasing status of the fetus trumps the interests that the woman may have in terminating the pregnancy.[74] While legally, this notion of the fetus having an increasing claim to protection does not translate into a differential permissibility of termination between the start of pregnancy and viability, from an ethical point of view one may find that the increasing moral status of the fetus makes termination morally less charged at around 16 than just prior to 24 weeks of gestation.

For those holding the view that the moral status of human fetuses increases with their development [75], FTAS serves a moral purpose by bringing down the average gestational age at which pregnancies are terminated because of fetal anomalies. For some women or couples, these moral considerations may implicitly or explicitly play a role in their personal decision-making, for instance when choosing to have an early termination for a condition diagnosed after FTAS, for which they would find it more difficult to terminate much later in pregnancy after STAS.

When asked about this difference in the IMITAS interviews, one woman said:

> "*I think, we are, I myself am, really very glad there was a scan at 13 weeks rather than one at 20 weeks, where this could be seen. Because then it would have been very difficult, don't you think?*" To which her partner added: "*Yes, yes. Sure, it had severe impairments, but*

many things were good. So I think that, at 20 weeks, one would really focus more on that, that one would think: yes but the brains are good and he has two arms, eh. Because it is more complete, and such a child has further developed."[49]

Another woman said:

"*And I think, when I see what came out [at birth], what eh, how it was fitted out with everything, it was really just eh, a human being. And then I think, yes, how is it at 20 weeks? So I think, both times it's awful, but I would rather have it earlier than eh, than with 20 weeks*".[50]

In the interviews, many more women expressed their views about why they considered later termination more difficult, not so much in terms of an increasing moral significance of the fetus as a separate entity, but rather of the increasing weight of their growing attachment to it. While this increased bonding is psychologically relevant, it also fits in with the ethical notion of a 'relationalist' rather than 'individualist' account of the moral status of the fetus.[76][51] When speaking about the ever stronger bond that they experience, especially after quickening (usually between 16-20 weeks), pregnant women not just express an emotion, but also make a value statement about their relation with the fetus as their (future) child. To the extent that this relationship gains weight, termination becomes more difficult, also morally.

For instance, one woman said:

"*So I think it is foremost the emotional connection that you have with it, that that is even greater [at 20 weeks], and now it is, yes I did not yet feel it [move], it is all still very small. Ehm, so that makes, I think, for me it would make a difference, I think. So I was very glad, or glad, I was, I felt it was a benefit, that it was found now and not only at eh 20 weeks*."[52]

Clearly, it would be a mistake to read these quotes as evidence for a concern that adding FTAS to the screening program might lead women to think more lightly about termination. Instead, FTAS enables termination at a gestational age where, according to widely shared and converging ethical views, the moral significance of that choice is not yet the same as later in pregnancy. If this leads to more pregnancies with fetal abnormalities being terminated than after STAS, there is no reason for regarding this outcome as problematic. Instead, it is in line with the aim of the screening if, with

[49] IMITAS interviews AFTER cohort, transcript #16.
[50] IMITAS interviews AFTER cohort, transcript #27.
[51] As explained by Lindsey Chambers: whereas "individualist accounts assume that entities can only have or lack moral status in virtue of their own features or properties, relationalist accounts (…) ground moral status in an entity's relation to other members of the moral community."[76] She adds that these concepts should be seen as overlapping and complementary, rather than as mutually exclusive.
[52] IMITAS interviews AFTER cohort, transcript #35.

FTAS, women are given the option of selective termination at a gestational age where this is, not just psychologically, but also morally, more acceptable to them.

A specific variant of the 'lower moral threshold' concern is that with FTAS women might more easily choose to terminate the pregnancy for less severe anomalies than after STAS. However, in the IMITAS data, there is no evidence for this. Nor did respondents in the survey among professionals recognized a trend in that direction. This is also what one would expect, given the emotional interest that women and couples have in their wanted pregnancies.

8.2 Disability rights critique

A further ethical debate that has accompanied the history of prenatal screening for fetal abnormalities concerns the acceptability of selective abortion. Those raising this issue are less worried about the fate of fetuses in prenatal screening than about how this practice might affect the lives of people living with the conditions screened for. According to representatives of the so-called 'disability rights critique', selective abortion is a eugenic practice, or at least a practice based on a discriminatory value judgement. It would send the message that those with the relevant disorders or handicaps have lives not worth living.[77, 78]

If meant as criticism of the motives of pregnant women or couples choosing selective termination when confronted with a diagnosis of a major fetal anomaly, this criticism is not convincing. When parents-to-be make this tragic decision, they may want to spare the child a life of suffering, or they may think that, given their circumstances, they would not be able to properly care for a child with a serious disorder. Or they may think about how this would change their own lives or the impact that it would have on the lives of their other children. When acting from such motives, they are certainly not making a discriminatory value judgement about disabled people. This shows again quite clearly in each and every of the IMITAS interviews with women or couples who had made the decision to terminate their pregnancies.

However, the criticism may be less easily dismissed if understood as directed against society as the instance behind the screening offer. The availability of the screening, the fact that it is paid for with public or collective money, the talk about termination as a conceivable option, all this would send the message that people with, for instance, Down syndrome or spina bifida, are less welcome in society. Also with regard to ultrasound screening, some argue that the whole practice comes with subtle societal pressure to prevent the birth of children with disorders and impairments.[79]

Against this criticism, one may refer to the official aim of screening for fetal anomalies, which is not eugenic prevention, but enabling women or couples to make meaningful reproductive decisions. However, to really prove the criticism wrong, it is not enough to wave the flag of official doctrine.

As remarked by the British geneticist and pediatrician Angus Clarke, it should show from all aspects of the design and presentation of the screening program that talk of this aim is not mere lip service.[80] This ranges from what women (couples) are told about the screening, to how information about test results is presented, to whether women of different backgrounds are helped to understand the choices they are facing in the light of their own values, to what support women are given when struggling with those choices, to how the screening is evaluated.

Part of the quality of the Dutch prenatal screening program is that, in comparison to how things are in some other countries, these aspects are relatively well guaranteed, with much attention to proper information and training of professionals. But there is no ground for complacency on this score. With prenatal screening becoming ever more complex, it remains a challenge to organize it in such a way that the implicit goals of the program[53] match its official aim. This should also be a leading consideration when deciding about how to implement FTAS as a further test in the program.

But the wider social policy context is important as well. As stated by the Health Council, the ideal of providing women (couples) with meaningful reproductive choices, is an illusion if they cannot trust society to also provide the conditions of care and integration that people with disorders and handicaps need in order to live meaningful lives.[12] The concern that appropriate care and facilities may actually be lacking, was echoed in some of the IMITAS-interviews.

[53] Implicit goals – term used by Clarke.[80]

9. Conclusions and recommendations

In this last section, we first phrase our conclusions as answers to the research questions that have guided the Ethics part of the IMITAS study, and will then end with recommendations.

9.1 Conclusions

> *Question 1: How does addition of a first-trimester anomaly scan (FTAS) affect the benefits-to-harms ratio of prenatal screening offer as a whole, for those to whom it is offered?*

As compared to screening in which STAS is the only fetal anomaly scan, screening with added FTAS comes with clear and important benefits. It enables a significant earlier diagnosis of major anomalies, including those that are 'always' (FTMA) and those that are 'often detectable' in the first-trimester, thus leading to more time for reproductive decision-making and earlier termination. As confirmed in the IMITAS study, the psychological impact of an early termination of pregnancy is lower than that of a late one. Women have a positive attitude to FTAS as a further screening test for fetal anomalies, and were found, at least in the context of the IMITAS study, to make an informed decision about having or not having the scan (sections 4.1, 4.2, and 5).

On the harms side, while FTAS means an extra test that as such contributes to the psychological burden of prenatal screening, this does not amount to a large adverse effect for most participants. However, for some of those confronted with prolonged uncertainty, including those with false positive findings that were initially confirmed, the harms may well exceed the benefits. Precisely with respect to their views and experiences, some data are still missing (section 4.2).

The pros and cons of adding FTAS to the screening program at 12+3-14+3 weeks as planned, cannot be seen in isolation from the impact that other first-trimester scans such as the dating scan already have on the number, nature and timing of prenatal diagnoses (section 4.3). As a consequence, two alternative scenarios may be considered: refraining from FTAS, and combining it with the dating scan at 10-12+6 weeks. As we have argued (section 6.2), the first of these scenarios is inherently problematic, if it amounts to regarding the dating scan (and other routine scans) as informal screening tests for fetal abnormalities. The second scenario comes with counseling challenges, as a result of combining tests that are offered for different purposes. Moreover, most major anomalies in the 'often detectable' category cannot yet be detected at the time of the dating scan, which renders both these scenarios (relying on the dating scan and combining with it) suboptimal when it comes to screening for all major anomalies rather than only for FTMA.

This leaves adding FTAS at 12+3-14+3 weeks the only serious option for consideration. With the above caveat concerning lack of data, we are inclined to conclude that the benefits-to-harms ratio of this new screening test is favorable. The benefits of avoiding, for as many women as possible, the

time pressure on diagnosis and decision-making that increasingly complicates prenatal diagnosis and counseling after STAS, are not easily overestimated.

A further improvement of the benefits-to-harms ratio of FTAS may still be possible. One should think here of a reconsideration of the referral protocol with an eye to finding the best balance of detecting major fetal anomalies as early as possible, while keeping the inevitable price in terms of false positives, uncertain outcomes and findings outside the target range as small as possible (section 6.1). Additionally, improvement may also be expected of a further learning curve of professionals involved in confirmatory diagnostic testing after FTAS referrals. The greater their uncertainty with regard to diagnosis and prognosis, the longer the diagnostic trajectories for women, including for those with false-positive findings.

> *Question 2: To what extent does the addition of this extra test fit in with the aim of the Program of Prenatal Screening for fetal abnormalities?*

The reason for adding FTAS to the prenatal screening program is not that this leads to finding more major structural anomalies than with STAS. Instead, the reason is that this leads to finding them earlier, so as to give pregnant women more time for reproductive-decision making. This makes perfect sense in the light of the atypical 'autonomy aim' of prenatal screening for fetal abnormalities, understood as helping women (or couples) make meaningful reproductive choices. In the light of this aim, it is also important that women were found to have made an informed decision about having or not having FTAS (section 5).

It is important to note that this was in the context of a testing offer that was explicitly presented to pregnant women as research. Should FTAS be introduced as a regular part of the screening program, women may be more inclined to see the scan as a routine element of obstetric care in pregnancy, which may influence the degree to which participation is based on an informed choice. The relatively low rate of informed choice for STAS in the Netherlands makes this a likely development.

The cases where FTAS comes with a proven preventative benefit are too few and far between to regard this as a separate aim of offering screening with this new first-trimester test (section 4.1)

> *Question 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?*

In wider debates about the ethics of prenatal screening, two themes have always been paramount: the acceptability of abortion, as seen from the perspective of the moral status of the fetus, and the acceptability of selective abortion, as seen from the perspective of the 'disability rights critique'.

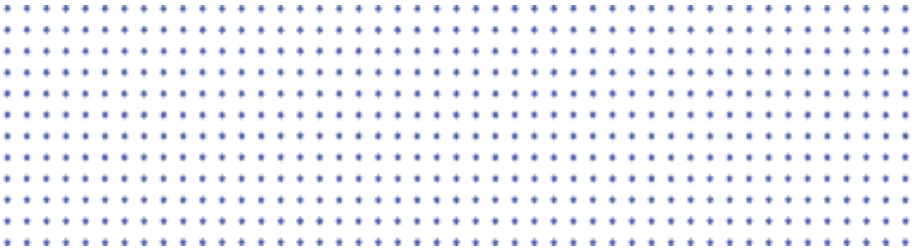
FTAS enables termination at a gestational age where, according to widely shared and converging ethical views, the moral significance of that choice is not yet the same as later in pregnancy. In the light of this, a conceivably higher termination rate after FTAS than STAS, should not be taken as evidence for a lower perceived moral threshold for termination. For a further concern about more terminations for less severe anomalies, there is no support from the IMITAS data. This is also what one would expect, given the emotional interest that women and couples have in their wanted pregnancies (section 8.1)

From the perspective of the 'disability rights critique', FTAS is only a further element in the discriminatory practice of prenatal screening and selective termination. The proper response to this charge is by making sure that all elements of the screening program reflect the aim of enabling women to make their own reproductive choices, rather than steering them towards termination when found to be carrying a fetus with an anomaly. Moreover, on a social policy level, appropriate conditions of care and integration should be in place for people living with disorders and handicaps (Section 8.2).

9.2 Recommendations

1. For a final assessment of the benefits-to-harms ratio of adding FTAS to the prenatal screening program, more data are needed with regard to the psychological impact of having a lengthy diagnostic trajectory due to uncertainty, and of being confronted with abnormal findings that were initially confirmed, but only later turned out to be false-positive. Part of this lacuna can quickly be filled up by conducting a further sub-analysis of the data of the IMITAS surveys for these specific groups. We recommend holding interviews with women confronted with these outcomes, as part of further research. We also recommend further research efforts to include perspectives of partners, and of women and their partners from underrepresented groups.
2. Whether the costs of adding FTAS to the prenatal screening program can be justified is a matter of just allocation of scarce financial resources. A further health-economic study, based on costs per case detected (not part of IMITAS) will be needed to inform this assessment. To avoid a morally problematic inequity of access, FTAS should ideally be offered free of charge.
3. FTAS should be considered a test for major anomalies, not just for FTMA. As such, it should not be offered at an earlier gestational age than was the case in the IMITAS study, which rules out the idea of combining FTAS with the dating scan.

4. Prior to the formal introduction of FTAS, the referral protocol should be re-evaluated, in the light of the findings of the IMITAS study, and with the aim of improving the benefits-to-harms ratio of FTAS as a test for major anomalies. This should be performed by a team of tertiary care specialists with expertise in post-test referrals and with knowledge of relevant international standards.
5. The fact that many major anomalies cannot yet be seen in the first-trimester is an inherent limitation of FTAS that requires realistic expectation management as part of pretest information and counselling, in order to avoid false reassurance. Women indicating that they would not have NIPT should be made aware of the fact that, although FTAS is not a test for chromosome abnormalities such as Down syndrome, it may still bring them to light.
6. While it seems too early to reconsider the IMITAS study policy to not refer incomplete scans when introducing FTAS, the contribution of this policy to the relatively large number of false-negative findings is a ground for concern. We recommend efforts aimed at improving the level of assessments so as to bring down the number of scans that are unnecessarily listed as incomplete. We also recommend a planned evaluation in due time of the non-referral policy, with an eye to optimizing the balance of false positives and negatives.
7. To allow for an expected learning curve with FTAS, it is too early to determine the future role of STAS in relation to this new screening test. Like FTAS, STAS should be considered a test for major anomalies, rather than for whatever anomalies it can reveal. More data about test-characteristics are needed, also for STAS.
8. Given the high rate of referrals for fetal anomalies resulting from the dating scan, women having that scan should be better prepared for the possibility that it may lead to such referrals, than is currently the case.



Abbreviations

FTAS	First-Trimester Fetal Anomaly Scan
FTMA	First-Trimester Major Anomalies, defined as: “severe structural anomalies that can be expected to be ‘always’ detected by FTAS”
IMITAS study	IMplementation of fIrst-Trimester Anomaly Scan
NIPT	Non-Invasive prenatal Test
NT	Nuchal translucency
STAS	Second-Trimester Fetal Anomaly Scan

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