Seeing the unseen

The importance of prenatal screening

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CHAPTER

13

GENERAL DISCUSSION AND *Future perspectives*

Seeing the Unseen: A wider scope

We started this thesis in an attempt to reveal, discover and comprehend the previously unseen or unrecognized features of the fetus while performing prenatal screening. By revealing and studying some of these hidden features and uncovering subtle details, with potentially great impact, we substantiate the importance of prenatal screening. However, given that some of the unseen will remain unseen, there are lingering questions that require our attention. In order to identify and answer these questions, we need to expand our perspective on "Seeing the Unseen", and that requires a broader scope, like putting a wider-angle lens to your camera. This widened scope does not just encompass scientific depths; it is a holistic view and encourages us to navigate into the societal aspects, innovative techniques and political aspects of prenatal screening.

In this exploration, we need to define why and how we screen within the present legal framework. Moreover, we need to consider the ethical dilemmas that often accompany prenatal screening with the choices of future parents, since they also have the right 'not to know' and not all variants on ultrasound are of significant importance. What groundbreaking technologies are on the horizon? From genomics to artificial intelligence, how can these tools revolutionize the accuracy of prenatal diagnosis? How do politicians and ethicists consider improvements in prenatal detection of fetal anomalies and what does it bring for future parents? We will elaborate and philosophize on these questions with the help of the evidence found in this thesis.

Societal aspects

Prenatal screening and its legal framework

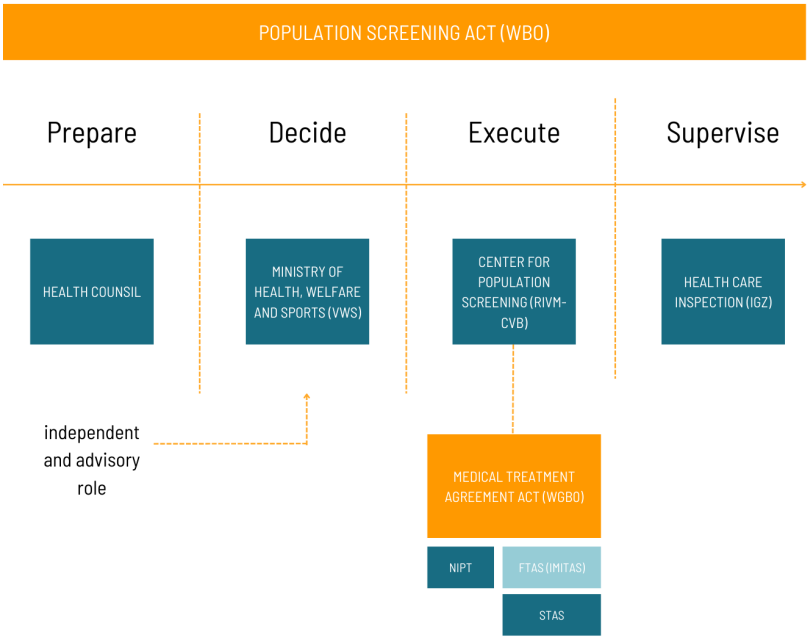
Prenatal screening for congenital anomalies encompasses the detection of a broad range of congenital anomalies[1,2,3,4] or subtle markers of genetic syndromes, detected in the early stages of pregnancy.[5-7] The World Health Organization (WHO) defines congenital anomalies as structural or functional abnormalities that occur during fetal development and can be identified before or after birth, sometimes even later in life.[8] These anomalies significantly impact individuals, families, healthcare systems, and societies due to their long-term effects. Congenital anomalies are an important predictor for health care consumption, the need for surgery and supportive therapy like physiotherapy or educational therapy in the first year of life and thereafter. Congenital anomalies can lead to lifetime disability, hindering participation in society and affect lifelong quality of life and economic productivity. Consequently, congenital abnormalities contribute significantly to the global burden of disease and result in substantial healthcare costs.[8] The primary aim of prenatal screening methods such as non-invasive-prenatal testing (NIPT) and structural ultrasound examinations is to inform future parents timely about the potential presence of congenital anomalies, thereby enabling them to make informed choices and promote reproductive autonomy.[9]

With the introduction of the national screening program in the Netherlands for all pregnant individuals in 2007, the availability and accessibility of prenatal screening for congenital anomalies increased. Screening, as defined by the Health Council, involves systematic early detection or exclusion of diseases or predispositions in a predefined group of individuals who do not have medical complaints. Prenatal screening differs from other screening methods, because it is tailored to the individual rather than the entire population, and does not take place in a prespecified age cohort but involves pregnant individuals who are receiving care from healthcare professionals.[9] Secondly, the aim to promote reproductive autonomy differs from the aim in breast or cervical cancer screening, which is primarily focused on disease prevention or health promotion.[10]

Due to the ability to screen for congenital anomalies during pregnancy, parents will face their own reproductive choices, which entail ethical and psychological consequences. Therefore, a crucial aspect is the concept of *Informed Choice* and *prefer not to know,* as outlined in the Medical Treatment Agreement Act (*Wet Geneeskundige Behandelingsovereenkomst, WGBO*). Future parents have the right to decide whether they wish to receive information on prenatal screening. Declining prenatal screening should also be respected as part of reproductive autonomy, acknowledging individuals' rights to decide whether they want to undergo testing and subsequently make reproductive decisions based on the results.[11] Certified counselors will continue to provide comprehensive details for those who wish to perceive information, so that well-informed choices can be made.[12]

The government imposes requirements on the execution of screening programs through the Population Screening Act (*Wet op het Bevolkingsonderzoek, WBO*) (Figure 1). Prenatal screening falls into the category of "population screening for serious diseases or abnormalities for which no treatment or prevention is possible", as described in the WBO. Fortunately, for the majority of congenital anomalies treatment is possible after birth. Prenatal screening also aims to identify fetus and children who would benefit from delivery in a setting where the right level of neonatal support is present. In the Netherlands, currently future parents are offered cell-free DNA (cfDNA) based genome wide-NIPT (GW-NIPT) as first tier test, a first trimester anomaly scan (FTAS) (IMITAS study) and a second trimester anomaly scan (STAS) as part of the national screening program. On behalf of the Ministry of Health, Welfare and Sports (VWS), the program is monitored and evaluated by the Center for Population Screening of the National institute for Public Health and Environment (RIVM/CVB). Besides the implementation of the program, the RIVM-CVB covers regulations regarding screening and training of sonographers with constant monitoring and evaluation of the quality of care.[9]

Figure 1. Legal framework of prenatal screening



Innovative techniques

Prenatal screening for chromosomal anomalies becomes prenatal diagnostics?

In most Western countries, cfDNA based NIPT is available as a second-tier test after first trimester combined testing (FCT) or increased risk due to maternal age.[13] In the Netherlands cfDNA based GW-NIPT is now offered as a first-tier test free of charge since April 2023, after careful scientific evaluation of the performance of NIPT in high risk (TRIDENT 1) and low risk (TRIDENT 2) pregnancies. CfDNA based NIPT offers a more accurate method for detecting fetal aneuploidies than traditional serum screening methods such as FCT and has the potential not only to screen for common trisomies, like targeted NIPT, but also rare autosomal trisomies and structural chromosomal aberrations of >10Mb[14-16]**.** The large majority of future parents prefer GW-NIPT[4], but currently still have the option to choose for targeted NIPT. From 2025 onwards, only GW-NIPT will be offered to pregnant individuals in the Netherlands.

Despite its accuracy, having cfDNA based NIPT as first tier test has some disadvantages. FCT was a risk-based method, which involved a detailed first trimester scan in combination with the concentration of β-hCG (free beta-human chorionic gonadotrophin) and PAPP-A (pregnancy-associated plasma protein A) levels in maternal blood. Unlike FCT, cfDNA based NIPT is a counting based method that is unable to detect triploidy due to the absence of proportional changes in the number of DNA fragments across the different autosomes. For early detection of triploidy,

ultrasound screening in the first trimester is crucial; if only cfDNA based NIPT is performed, detection might not occur before 20 weeks of gestation. It is of importance to determine whether the origin of the haploid set is maternal (digynic) or paternal (diandric). The paternally derived triploids are partial molar pregnancies and can progress into gestational trophoblastic neoplasia (GTN). Since triploid pregnancies have unique sonographic features that allow for determination of the parental origin[7], first trimester ultrasound screening should have its own place alongside GW-NIPT in the current national screening program.

A recent approach showed that single-nucleotide polymorphism (SNP) based NIPT can identify the presence of additional fetal haplotypes, indicative of a triploid or dizygotic multifetal pregnancy, and even determines parental origin.[17,18] If SNP based NIPT identifies an extra haplotype and ultrasound examination is negative for viable twins, vanishing twins or fetal death, the predictive value for triploidy testing could reach 43%.[19] For cases where ultrasound findings are in line with triploidy, the predictive value will even be higher.[7] Detecting diandric or digynic triploidy via SNP based NIPT reduces the necessity for future parents to undergo invasive genetic testing. It even suggests that DNA analysis during pregnancy or after termination might be unnecessary if the diagnosis is made prenatally. At the patients' level, this allows for adequate time for optimal counseling regarding the diagnosis and the termination approach, potentially resulting in earlier termination of pregnancy (TOP) and subsequently fewer psychological consequences.[20] At population level, this contributes to reduced healthcare costs and more sustainable care.

Early Nuchal Translucency screening

With the tendency to replace FCT by cfDNA based NIPT in the western world, the chance to perform a nuchal translucency (NT) measurement forfeits. Besides, cfDNA based NIPT cannot cover the wide spectrum of genetic anomalies that are potentially linked to an increased NT. In a retrospective study involving 226 patients with a NT measurement above 3.5mm (99th centile), targeted NIPT would have detected only 80% of the genetic anomalies, and even with GW-NIPT, only 88% would have been detected.[21] In a larger study involving 1901 pregnancies, 9% of genetic anomalies would not have been detected by cfDNA based NIPT.[22] Because of the various genetic anomalies related to an increased NT, invasive testing rather than cfDNA is offered when NT measures ≥3.5mm from 11 and 2 weeks of gestation onwards. However, performing an NT measurement before this time seems to be vital given the association between an early increased NT and adverse pregnancy outcome.[6] NT measurement at the dating scan could serve as the first step in a prenatal screening program. We advise to measure the measure the NT at the dating scan if it is enlarged by eyeballing. In case of an enlarged NT ≥2.5 mm before 11 weeks gestation (CRL=45 mm) we advise to refer to a Fetal Medicine Unit for further detailed sonography and pre-test invasive counseling before offering solely cfDNA based NIPT.

Currently, a first trimester anomaly scan at 11-14 weeks including NT measurement is carried out as part of the IMITAS-study. This scan could be seen as an additional opportunity to reevaluate the NT, instead of referring immediately after a NT ≥2.5mm seen at the dating scan. However, these cases should be referred directly to a Fetal Medicine Unit for invasive diagnostics to avoid disadvantaging parents that were only offered cfDNA. This proactive approach is necessary due to the significant association between early increased NT and adverse pregnancy outcomes, even if the NT normalizes after 13 weeks.[6]

Genetic testing, what should we offer future parents?

Pre-test counseling becomes more important with the implementation of solely GW-NIPT from 2025 onwards, given the increasing screen positive rate for chromosomal aberrations and the decreasing predictive value thereof.[4,23] Additionally, post-test counseling in case of these findings is equally important and is carried out by a clinical geneticist. Future parents will receive information on the test results and offered follow up diagnostic testing to assess the clinical significance of the finding.
When a congenital anomaly is detected by ultrasound screening, invasive diagnostic testing is generally offered. Aneuploidy, copy number variations (CNV's), single nucleotide variations (SNVs), and insertions and deletions are examples of a possible underlying cause of a congenital anomaly. If desired by future parents, standard test performed are rapid aneuploidy testing (QF-PCR) and chromosomal microarray analysis (CMA) thereafter. However, we found that many genetic variations are beyond the scope of CMA detection[24] and other recent research indicates that whole exome sequencing (WES) offers a higher diagnostic yield.[25,26] A recent systematic review that included 4350 fetuses demonstrated that the diagnostic yield of WES for structural anomalies among included studies ranged from 5% to 89%. The combined additional yield of WES over CMA or karyotype was approximately 31%.[26] Thus, WES provides additional diagnostic yield of genomic variants in CHD[24] but also in other structural anomalies.[25,26]

To examine the genetic makeup of fetuses with structural anomalies is crucial for prenatal genetic counseling and risk assessment. However, the high diagnostic yield of WES prompts the question: should it be universally offered to all future parents when a congenital anomaly is detected? WES is more expensive than CMA, and some are concerned about the potential rise in healthcare costs if universally provided. Nonetheless, more children with a DNA diagnoses will be labeled prenatally and likely more pregnancies will be terminated once detailed counseling can be done on the severity of the DNA diagnosis. If these pregnancies would have been continued, these children would have had a lifelong high healthcare consumption. Future studies will have to address the benefits of WES and potentially explore the cost-effectiveness of WES. As due to the significant link between genetic diagnosis and CHDs, we strongly advocate for offering WES in cases involving severe CHD.

Anomaly screening meets artificial intelligence

We found that eliminating the FCT from the prenatal screening program had consequences for the early detection of severe congenital heart defects (CHD), such as atrioventricular heart defects (AVSD) and hypoplastic left heart syndrome (HLHS). We hypothesized that with the introduction of a first trimester anomaly scan the early detection of these anomalies will likely increase. However, the first trimester detection of CHD is challenging due to the small size of the heart, frequent unfavorable fetal positioning and involuntary movements and hesitancy to use vaginal ultrasound. AI could possible resolve these disadvantages by recognizing the standard planes necessary for fetal echocardiography assessment and thereby increasing CHD detection rate.[27] Besides, it could reduce examination time and physician workload. In second trimester, a deep learning method to visualize and detect heart substructures in 2D screening videos already exist. It generates an abnormality score based on deviations from normal and resulted in notable increase in CHD detection by sonographers.[28] Another AI supported system is based on automatically retrieved right and left outflow tracts from a three-dimensional volume of the fetal chest, and achieved accurate identification rates of 91.7% and 94.4%, respectively.[29]

Political aspects

Ethical dilemmas: parent's choices

Despite the enhanced detection rates of congenital anomalies[30,31] evolving in-utero treatments[32-34] and innovative techniques, parents are facing a reproductive choice; to continue pregnancy or choose for termination of pregnancy (TOP)? The autonomy of the patient is essential, and empathic healthcare providers who offer non-judgmental and compassionate care can greatly enhance parents' satisfaction in case of TOP.[35] Besides, early TOP is associated with less reported grief and a lower maternal mortality rate.[20]

As today, 60% of women of reproductive age are living in regions where TOP is not prohibited, but 40% still live under restrictive abortion laws.[36] In countries where TOP is permitted, there are discrepancies in regulations and definitions regarding the types of anomalies for which termination is allowed.[36] Despite being legal in the Netherlands, TOP remains part of the Criminal Code under article 296. This legal framework makes anyone performing TOP potentially punishable, except in specific circumstances outlined in the Termination of Pregnancy Act (*Wet afbreking zwangerschap, WAZ*) [37]. Currently, TOP is not a right, but rather a criminal offense with specific exceptions. The aim should be to recognize TOP as essential healthcare rather than a criminal act and we should strive for its removal from the Criminal Code.

By Dutch law, TOP is allowed until 24 weeks of gestation weeks and 6 days of gestation by *WAZ*.[37] After 24 weeks of gestation, late termination of pregnancy (LTOP) is only possible if the mothers'

life is in danger or if the fetus has anomalies that are incompatible with life (category 1) or if the anomalies lead to irreversible functional impairments or a reasonable expectation of limited chances of the unborn child's survival (category 2).[38] Physicians that are involved in LTOP or engage in life-ending actions for newborns face legal repercussions. It is mandatory to report all category 2 cases to a central committee of experts appointed by the Minister of Health, Welfare and Sports and the Minister of Justice. The committee assesses, based on criteria, whether a physician has acted medically and carefully in category 2 cases. Only if the committee deems the termination as not careful, a second assessment by the Public Prosecutor's Office is necessary.[39]

Physicians in the Netherlands often find the regulations meaningful, but they find the possibility of prosecution, the high administrative burden, and the emotional toll burdensome, also for the parents.[40] At present, every year patients are referred to Belgium[39], where there is no legal limit for TOP in case of severe anomalies after a positive verdict form an internal medical ethical committee. Despite these challenges, the evaluation of all LTOP cases in the Netherlands 2023, revealed that all physicians acted in accordance with the criteria and no one was prosecuted.[41] By publicizing LTOP cases, the committee aims to provide transparency and confidence among physicians and parents considering LTOP.[41] Their goal is to increase information provision for parents and physicians, especially considering that some cases referred to Belgium could have been managed in the Netherlands.[39]

We deem that is important that parents and physicians know that LTOP is a possibility in the Netherlands under certain circumstances.[39] Based on our study, we found that identifying a severe isolated congenital heart anomaly (CHD) at an early stage trough an additional first trimester scan made parents more inclined to consider termination of the pregnancy, but had no effect on the gestational age of termination.[42] Parents undergo a thoughtful decision making process, often aided by healthcare professionals, before opting for TOP.

Afterthought

In essence, "Seeing the Unseen" in prenatal screening invites us to remain a wide scope by not only have the focus on the scientific complexities of the unseen aspects of the fetus but also comprehends the technological, ethical, social and even political dimensions. With all the upcoming new technologies, improvements in prenatal screening and extensive genetic testing, pre-and post-test counseling becomes increasingly important and difficult. By recognizing these challenges, and answering questions with the help of research by including physician's perspectives alongside patient's perspectives, we pave the way for a future where every expectant parent can make choices based on their own values and believes, with caretakers that will inform and support.

References

1. Salomon LJ, Alfirevic Z, Berghella V, et al. ISUOG Practice Guidelines (updated): performance of the routine mid-trimester fetal ultrasound scan. *Ultrasound Obstet Gynecol.* 2022;59(6):840-856.
2. Bilardo CM, Chaoui R, Hyett JA, et al. ISUOG Practice Guidelines (updated): performance of 11-14-week ultrasound scan. *Ultrasound Obstet Gynecol.* 2023;61(1):127-143.
3. Oepkes D, Page-Christiaens GC, Bax CJ, et al. Trial by Dutch laboratories for evaluation of non-invasive prenatal testing. Part I-clinical impact. *Prenat Diagn.* 2016;36(12):1083-1090.
4. van der Meij KRM, Sistermans EA, Macville MVE, et al. TRIDENT-2: National Implementation of Genome-wide Non-invasive Prenatal Testing as a First-Tier Screening Test in the Netherlands. *Am J Hum Genet.* 2019;105(6):1091-1101.
5. Snijders RJ, Noble P, Sebire N, et al. UK multicentre project on assessment of risk of trisomy 21 by maternal age and fetal nuchal-translucency thickness at 10-14 weeks of gestation. Fetal Medicine Foundation First Trimester Screening Group. *Lancet.* 1998;352(9125):343-346.
6. Lugthart MA, Bet BB, Elsman F, et al. Increased nuchal translucency before 11 weeks of gestation: Reason for referral? *Prenat Diagn.* 2021;41(13):1685-1693.
7. Lugthart MA, Horenblas J, Kleinrouweler EC, et al. Prenatal sonographic features can accurately determine parental origin in triploid pregnancies. *Prenat Diagn.* 2020;40(6):705-714.
8. (WHO) WHO. Congenital anomalies. [Internet]. 2016; Available from: https://www.who.int/news-room/fact-sheets/detail/congenital-anomalies.
9. RIVM. Draaiboek Prenatale Screening. In: Bilthoven: Rijkinstituut voor Volksgezondheid en Milieu; 2023.
10. Holland WW, Stewart S, Cristina M. Policy brief screening in Europe. In: Europe WHOoboTEOoHSaPWROf, ed2006.
11. Kater-Kuipers A, de Beaufort ID, Galjaard RH, et al. Rethinking counselling in prenatal screening: An ethical analysis of informed consent in the context of non-invasive prenatal testing (NIPT). *Bioethics.* 2020;34(7):671-678.
12. Michie S, Dormandy E, Marteau TM. The multi-dimensional measure of informed choice: a validation study. *Patient Educ Couns.* 2002;48(1):87-91.
13. Gadsbøll K, Petersen OB, Gatinois V, et al. Current use of noninvasive prenatal testing in Europe, Australia and the USA: A graphical presentation. *Acta Obstetricia et Gynecologica Scandinavica.* 2020;99(6):722-730.
14. Gil MM, Galeva S, Jani J, et al. Screening for trisomies by cfDNA testing of maternal blood in twin pregnancy: update of The Fetal Medicine Foundation results and meta-analysis. *Ultrasound in Obstetrics & Gynecology.* 2019;53(6):734-742.
15. Judah H, Gil MM, Syngelaki A, et al. Cell-free DNA testing of maternal blood in screening for trisomies in twin pregnancy: updated cohort study at 10–14 weeks and meta-analysis. *Ultrasound in Obstetrics & Gynecology.* 2021;58(2):178-189.
16. Rose NC, Barrie ES, Malinowski J, et al. Systematic evidence-based review: The application of noninvasive prenatal screening using cell-free DNA in general-risk pregnancies. *Genet Med.* 2022;24(9):1992.
17. Samango-Sprouse C, Banjevic M, Ryan A, et al. SNP-based non-invasive prenatal testing detects sex chromosome aneuploidies with high accuracy. *Prenatal Diagnosis.* 2013;33(7):643-649.
18. Pergament E, Cuckle H, Zimmermann B, et al. Single-nucleotide polymorphism-based noninvasive prenatal screening in a high-risk and low-risk cohort. *Obstetrics and Gynecology.* 2014;124(2 PART1):210-218.
19. Kantor V, Jelsema R, Xu W, et al. Non-invasive prenatal screening for fetal triploidy using single nucleotide polymorphism-based testing: Differential diagnosis and clinical management in cases showing an extra haplotype. *Prenat Diagn.* 2022;42(8):994-999.
20. Korenromp MJ, Christiaens GCML, van den Bout J, et al. Long-term psychological consequences of pregnancy termination for fetal abnormality: a cross-sectional study. *Prenatal Diagnosis.* 2005;25(3):253-260.
21. Miranda J, Paz y Miño F, Borobio V, et al. Should cell-free DNA testing be used in pregnancy with increased fetal nuchal translucency? *Ultrasound in Obstetrics & Gynecology.* 2020;55(5):645-651.
22. Bardi F, Bosschieter P, Verheij J, et al. Is there still a role for nuchal translucency measurement in the changing paradigm of first trimester screening? *Prenatal Diagnosis.* 2020;40(2):197-205.
23. Benn P, Grati FR. Genome-wide non-invasive prenatal screening for all cytogenetically visible imbalances. *Ultrasound in Obstetrics & Gynecology.* 2018;51(4):429-433.
24. van Nisselrooij AEL, Lugthart MA, Clur SA, et al. The prevalence of genetic diagnoses in fetuses with severe congenital heart defects. *Genet Med.* 2020;22(7):1206-1214.
25. Hu P, Zhang Q, Cheng Q, et al. Whole genome sequencing vs chromosomal microarray analysis in prenatal diagnosis. *Am J Obstet Gynecol.* 2023;229(3):302.e301-302.e318.
26. Mellis R, Oprych K, Scotchman E, et al. Diagnostic yield of exome sequencing for prenatal diagnosis of fetal structural anomalies: A systematic review and meta-analysis. *Prenatal Diagnosis.* 2022;42(6):662-685.
27. Ungureanu A, Marcu A-S, Patru CL, et al. Learning deep architectures for the interpretation of first-trimester fetal echocardiography (LIFE) - a study protocol for developing an automated intelligent decision support system for early fetal echocardiography. *BMC Pregnancy and Childbirth.* 2023;23(1):20.

28. Sakai A, Komatsu M, Komatsu R, et al. Medical Professional Enhancement Using Explainable Artificial Intelligence in Fetal Cardiac Ultrasound Screening. *Biomedicines.* 2022;10(3):551.
29. Abuhamad A, Falkensammer P, Reichartseder F, et al. Automated retrieval of standard diagnostic fetal cardiac ultrasound planes in the second trimester of pregnancy: a prospective evaluation of software. *Ultrasound in Obstetrics & Gynecology.* 2008;31(1):30-36.
30. Boyd PA, Devigan C, Khoshnood B, et al. Survey of prenatal screening policies in Europe for structural malformations and chromosome anomalies, and their impact on detection and termination rates for neural tube defects and Down's syndrome. *Bjog.* 2008;115(6):689-696.
31. Pan M, Huang LY, Zhen L, et al. A cost-effectiveness analysis comparing two different strategies in advanced maternal age: Combined first-trimester screening and maternal blood cell-free DNA testing. *Taiwan J Obstet Gynecol.* 2018;57(4):536-540.
32. Hecher K. Intrauterine surgery: how far we have come in 30years. *Ultrasound Obstet Gynecol.* 2021;57(1):22-24.
33. Deprest JA, Nicolaides KH, Benachi A, et al. Randomized Trial of Fetal Surgery for Severe Left Diaphragmatic Hernia. *N Engl J Med.* 2021;385(2):107-118.
34. Joyeux L, De Bie F, Danzer E, et al. Learning curves of open and endoscopic fetal spina bifida closure: systematic review and meta-analysis. *Ultrasound in Obstetrics & Gynecology.* 2020;55(6):730-739.
35. Heaney S, Tomlinson M, Aventin Á. Termination of pregnancy for fetal anomaly: a systematic review of the healthcare experiences and needs of parents. *BMC Pregnancy and Childbirth.* 2022;22(1):441.
36. Rights CfR. The World's Abortion Laws. 2023; https://maps.reproductiverights.org/worldabortionlaws.
37. W.M. Ankum, G. Kleiverda, S. Rombout de Weerd, et al. Herziene NVOG-richtlijn ' Zwangerschapsafbreking tot 24 weken. 2015:1-22.
38. Pajkrt E, Manten GTR, Coumans ABC. Model protocol Medisch handelen bij late zwangerschapsafbreking :Nederlandse vereniging voor obstetrie en gynaecologie;. In:2017
39. ZonMW. Evaluatie regeling late zwangerschapsafbreking en levensbeeindiging bij pasgeborenen. In:2022.
40. van de Vathorst S, Gevers JKM, van der Heide A. Evaluatie regeling centrale deskundigencommissie late zwangerschapsafbreking en levensbeëindiging bij pasgeborenen. In: ZonMW, ed2013.
41. pasgeborene Blzelb. Jaarverslag late zwangerschapsafbreking en levensbeeindiging bij pasgeborenen. In:2021.
42. Lugthart MA, Verbaarschot E, van Nisselrooij AEL, et al. Early Detection of Isolated Severe Congenital Heart Defects Is Associated with a Lower Threshold to Terminate the Pregnancy. *Fetal Diagn Ther.* 2023;50(4):248-258.