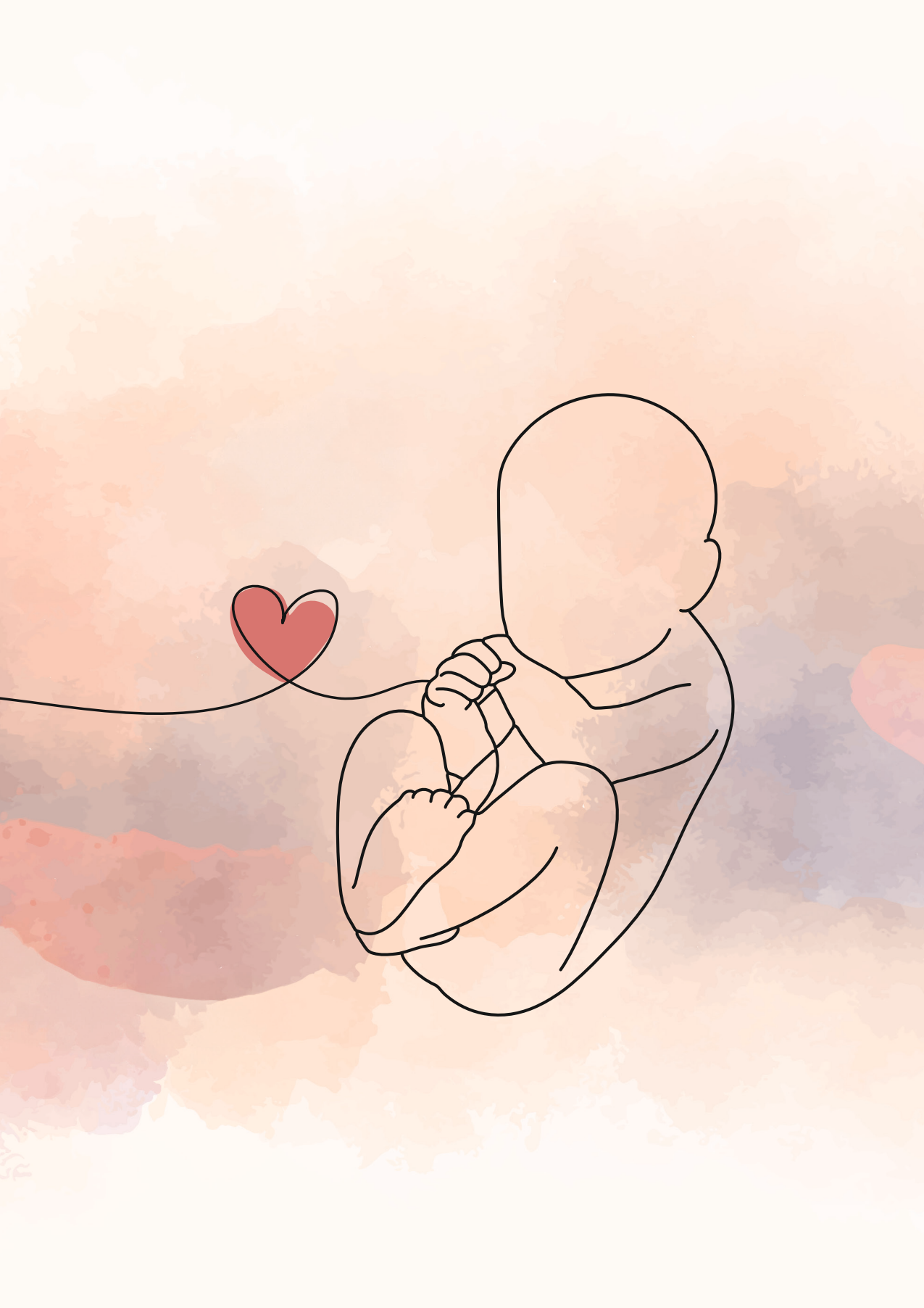
Congenital heart defects: from a prenatal perspective

Nisselrooij, A.E.L. van



CHAPTER 9

General discussion

Recent innovations in ultrasound technology and the increase in expertise have caused a rapid elevation in prenatal detection rates for congenital heart defects. Prenatal detection is nowadays possible at an early gestational age. These developments, however, also raised challenges for prenatal counseling. This thesis focuses on several aspects of screening for congenital heart defects (CHD) in the fetus and on the establishment of the prognosis following prenatal CHD diagnosis. To improve the performance of screening, chapter 2 in this thesis displays potential (adjustable) risk factors for a missed prenatal diagnosis. Other studies in this thesis elaborate on the prognosis of CHD from a fetal perspective, as we have shown that this may vary significantly from the prognosis following a postnatal diagnosis or the prognosis after an intervention. This chapter will elaborate on several aspects in the care for fetuses with CHD. This can roughly be divided into three main themes: the prognosis of a CHD at mid-gestation, the performance of prenatal screening and ethical considerations regarding screening for CHD.

PROGNOSIS OF A CONGENITAL HEART DEFECT AT MID-GESTATION

Prenatal detection of cardiac anomalies has - with the development of structural screening programs - significantly increased over time. The prognosis of early diagnosed congenital heart defects, particularly in the fetal period, may, however, be challenging to determine. This prognosis is mainly based on the reported outcome in cohort studies. The majority of these cohort studies, however, concern a specific cardiac defect, following cardiac surgery or a cardiac intervention. The postoperative or post-intervention prognosis differs from the prognosis at mid-gestation for two reasons. First of all, the time-interval from mid-gestation to postnatal intervention is considerable and significant changes or complications may have occurred. Secondly, the prognosis may differ due to the fact that prenatally detected and undetected cases may not be similar at baseline. Variation in these study populations occurs because some cases result in spontaneous fetal demise, in some cases parents may opt for pregnancy termination and some newborns die after birth before surgery or cardiac interventions have been performed. Thus, fetuses diagnosed with a CHD at mid-gestation in general comprise a significantly different population with a more severe phenotype compared to those diagnosed and followed up after birth. Therefore, the studies in this thesis specifically focus on the outcome of fetal congenital heart defects to gather more knowledge on the prognosis at this time of diagnosis to improve prenatal counseling.

One of the major determinants for prognosis is the presence of a genetic syndrome in CHD cases. It is generally known that congenital heart defects are strongly associated with genetic diagnoses, which increase the risk of fetal demise or postnatal complications. Fetal studies that report on the incidence of genetic diagnoses, beyond

screening for aneuploidy or 22q11.2 deletion syndrome, are scarce. In Chapter 3 we studied the incidence of genetic anomalies in the largest cohort of euploid fetuses with CHD so far and assessed the impact on several outcome parameters. This study showed that 16% of isolated and non-isolated euploid CHD fetuses were diagnosed with a genetic diagnosis following microarray analysis or exome sequencing. In this cohort, the presence of these additional genetic diagnoses increased the risk of fetal growth restriction, premature birth, mortality and developmental delay. Based on the results from this large unselected cohort of CHD fetuses, the presence of genetic diagnoses does not only occur more often in fetuses diagnosed at mid-gestation compared to children with CHDs, but it had significantly impact on the prognosis as well. It is therefore likely that the increased incidence of cases with genetic anomalies is an important contributor to the differences in prognosis between fetal and postnatal cohorts. Our study shows that knowledge on the presence or absence of genetic anomalies at time of mid-gestational diagnosis is essential for prenatal counseling to estimate the prognosis for the child. The estimation of prognosis in these children does not only involve the presence of neurodevelopmental delay, but the chance of survival as well. Further research to determine the incidence of specific genetic variants for each congenital heart defect separately from a fetal perspective is necessary to enable patient-specific counseling on the indication for additional genetic testing.

A very important prognostic factor for parents is (the risk of) neurodevelopmental delay, which has a major impact on the quality of life. Neurodevelopmental delay occurs in at least one third of children with complex CHD. Existing literature indicates that this delay may start in utero. In Chapter 5, we studied head growth as a marker for neurodevelopment in CHD fetuses. Our findings reveal that not only head growth, but overall growth is impaired in fetuses with CHD. Although fetal growth measurements often fall within normal limits, they are significantly smaller compared to healthy fetuses. This indicates that CHD fetuses generally do not achieve their growth potential. Intrauterine growth restriction appeared particularly caused by impaired placentation and to a lesser extent by genetic syndromes. The risk of placenta-related pathology is increased in fetuses with congenital heart defects. Consequently, there is an increased incidence of preeclampsia, lower birthweight and a higher rate of small for gestational age neonates. [1, 2] While these measurements could not directly be related to neurodevelopmental outcome in our studies, previous literature shows that (early) fetal growth restriction is associated with neurodevelopmental delay.[3] Therefore, impaired placentation and subsequently impaired fetal growth may have a significant influence on delayed neurodevelopment in CHD fetuses. Future research on brain development in CHD fetuses and infants should be related to overall fetal growth and additional pathology.

The significant difference in prognosis between prenatally detected and postnatally detected cases was also demonstrated in specific cardiac diagnoses. In Chapter 7 we report on the first relatively large cohort study that evaluates prognosis of a common arterial trunk from a fetal perspective. A systematic review was performed to include additional cases. Our results show that the risk of mortality in fetuses diagnosed with CAT is significant. In a considerable number of pregnancies with fetal common arterial trunk, the parents decided to terminate the pregnancy, mainly in cases with concomitant comorbidity or significant genetic syndromes. Despite this, still 40% of continuing pregnancies with an intention-to-treat resulted in fetal or postnatal demise and only 30% of survivors did not show signs of additional morbidity or developmental delay at the age of six. Postnatal cohort studies, on the other hand, generally tend to depict a more optimistic prognosis, with 1-year survival rates between 80 and 90%. This is comparable to the postoperative survival rate of 87% in our cohort, if we solely include cases that underwent surgery. This difference can be explained by the fact that demise mainly occurred in utero or shortly after birth, due to truncal valve incompetence or other complications as a result of a genetic syndrome, in particular when delivered prematurely. These results emphasize that characteristics at diagnosis (genetic diagnoses, extra-cardiac comorbidity etc.) and associated outcome parameters (complications due to risk of premature birth or genetic syndrome, mortality) are strongly correlated to - and significantly differ with - the time of diagnosis.

Chapter 8 of this thesis focuses on the prognosis of an aorto-left ventricular tunnel (ALVT), an extremely rare congenital heart defect. We initiated a retrospective multicenter study on this particular defect, due to the diagnosis of ALVT in a fetus of 20 weeks' GA in our own center. The dilatation and poor contractility of the left ventricle was impressive, but prenatal counseling on the prognosis was hampered by the scarce literature on this diagnosis in fetuses. The internationally collected fetal cases were combined with a systematic review of the literature, which resulted in a total of 42 fetuses with ALVT. This study shows that 40% of fetuses with ALVT results in fetal or neonatal demise before a viable age was reached or surgery could be performed. Not surprisingly, symptoms of fetal hydrops (such as ascites, pleural effusion or skin edema) were present in all cases resulting in fetal demise. On the other hand, the fetuses that did not develop hydrops before 24 weeks' GA, all made it to term, received corrective surgery and were alive without additional morbidity at the age of 3. Similar to our findings, a review of cases in the literature showed that in the absence of hydrops, fetal or neonatal mortality rarely occurred. These findings are extremely important for prenatal counseling, as it indicates that stable non-hydropic fetuses with ALVT generally survive to term with good clinical outcome, despite the impressive cardiomegaly and

impaired contractility. Counseling should therefore clearly address that the prognosis at mid-gestation highly depends on the presence of hydrops at that time.

Lastly, a prenatal diagnosis does not always equal the diagnosis after birth. First of all, errors in the cardiac diagnosis can explain some of these differences, for several reasons. Secondly, some CHDs simply do not become apparent until the third trimester or even develop in the postnatal period. In Chapter 6 we describe the outcome of cardiac ventricular size disproportion at mid-gestation. It is well known that this feature is a marker in fetal life for the development of aortic coarctation after closure of the arterial duct in the first days of life. Although prenatally counseled to be at risk for the development of aortic coarctation, only 40% truly develop an aortic coarctation. Prenatal counseling addresses the risk of coarctation, as well as the considerable risk of a false-positive finding. However, the clinical course of this group had never been studied before. In Chapter 6 we specifically focused on these false-positive cases. Amongst those that did not develop aortic coarctation, a large proportion of these neonates showed prenatally undetected congenital defects (46%) and/or pulmonary or transition problems (35%) during postnatal follow-up. Only 45% of these cases did not need any medical service in the neonatal period, nor did they require medication, postnatal intervention or surgery at all.

It is well-known that cases at risk for aortic coarctation are one of the most difficult to identify in the fetus. Due to the low detection rate for aortic coarctation, together with the high number of false positives, the majority of studies have primarily focused on enhancing detection rates and differentiating coarctation cases from those that appear 'normal' after birth. The results from our study have shown that literature should not solely focus on the 'true' aortic coarctation cases, as those that do not develop aortic coarctation are still at significant risk of transitional problems after birth, that may require intensive care or present with other congenital defects. Close observation should therefore be warranted, regardless of the initial postnatal diagnosis, and equally represented in the literature to improve counseling on prognosis of true- and false-positive cases.

These results emphasize that referencing postnatal studies for prenatal counseling should be avoided or done with caution, as it might present a falsely optimistic perspective and result in a significant overestimation of the prognosis at mid-gestation. Due to rapid innovations in the care for and outcome of fetus and neonates with CHD, additional research should not merely elaborate on (postoperative) survival, but gather evidence on long-term outcome and wellbeing in general as well.

In conclusion, fetuses with a CHD at mid-gestation comprise a significantly different population compared to those diagnosed or studied after birth. Postnatal cohorts represent only a selected proportion of all fetuses diagnosed with CHD at mid-gestation. These selected cases generally have a better chance of survival and prognosis after birth, due to a lower incidence of genetic diagnoses or associated risks, such as premature birth and comorbidities. Although evidence on the prognosis of CHD from a fetal perspective is essential, the availability is still limited. To enhance prenatal counseling, further research from a fetal perspective is necessary to provide a more accurate and patient specific estimation of prognosis and quality of life, including long-term outcome in general. Until then, counsellors and scientists should be aware of this significant selection bias and statements regarding the expected prognosis should be made with caution.

IMPROVEMENT OF PRENATAL SCREENING FOR CHD

Prenatal detection of CHD remains a hot topic in current literature, with the aim to optimize timely treatment of these significant defects. Despite multiple interventions to improve detection rates, including a standardized approach to assess the cardiac anatomy and the addition of the three-vessel trachea view, still a considerable number of cases is missed antenatally. Prenatal detection rates for congenital heart disease range from 30-60% in developed countries, but have generally increased over time. The detection rate of critical or significant heart defects is much higher, with a detection rate for single ventricular anomalies of almost 100% in countries with well-organized screening programs nowadays. If additional extracardiac malformations are present, the likelihood of antenatal detection of CHD also increases. The use of a systematic approach with mainly transversal planes, including the four-chamber view, left and right ventricular outflow tracts, three-vessel view and three-vessel-trachea view, has become standard practice to structurally assess the fetal heart and maximizes the cost-effectiveness of prenatal screening.[4, 5] However, isolated heart defects that present with a normal four-chamber view, such as transposition of the great arteries or aortic coarctation, remain easily missed.[6, 7] In this section, we will further discuss risk factors for an antenatal miss and elaborate on potential strategies to improve prenatal detection rates in the future.

Current literature reports numerous studies that aim to develop strategies to improve prenatal detection rates. Little is known about factors that contribute to or cause antenatal miss in these cases. In the PRECOR registry, all fetus or children with a diagnosis of a severe congenital heart defect have been registered since 2002. We identified all undetected and detected cases in PRECOR to study impeding factors

and potential causes for an antenatal miss by gathering their original ultrasound scans (Chapter 2). The results of this study have shown that the quality of cardiac planes obtained during the standard anomaly scan was significantly better in detected compared to undetected cases and increased with the number of ultrasound scans performed by a sonographer per year. While assessing potential causes of a missed prenatal diagnosis, we observed that in half of the undetected cases the cardiac planes had not technically been obtained adequately, resulting in images of insufficient quality to visualize the cardiac defect. In 30% of undetected cases, however, the images were of sufficient quality to visualize the defect, but the CHD had not been recognized by the sonographer. It was thought that a missed prenatal diagnosis was inevitable in the remaining 20%, as the quality was sufficient, but the cardiac anatomy appeared normal at mid-gestation. This information is essential to identify and address determinants for a prenatal diagnosis to further improve antenatal detection of CHD.

The main cause for an antenatal miss appeared a lack of competence to obtain technically correct cardiac images in abnormal cases, although sonographers were capable to produce these images in normal cases. Previous literature has shown that education and specific hands-on training programs to acquire satisfactory views has a positive impact on the quality of the structural anomaly scan. These studies, however, were able to improve detection rates for CHD up to 60%, which equals the current detection in an increasing number of Western countries, including the Netherlands. It is therefore questionable whether increasing the amount of training could further improve current detection rates in these countries. The international guidelines available to standardize quality, obligatory training programs to become and/or stay qualified as a sonographer and routinely performed monitoring audits are all focused to improve and guarantee adequate quality of screening in a normal setting.[8-11] However, it seems that we do not train our sonographers how to adapt to the abnormal setting and how to enable them to acquire competent views in those cases as well. There could be various psychological reasons for sonographers to perform well in normal cases, but not show similar capability in abnormal cases. This could be attributed to specific personality traits, such as tolerating suboptimal images occasionally, or due to limited experience, causing sonographers to rather question their own abilities rather than the fetus's anatomy.

In Chapter 2, we also found that the quality of cardiac scans in abnormal cases increased with the volume of ultrasound scans performed by the sonographer and the yearly volume of scans in the screening center. This correlation is a probably a result of multiple factors. First of all, sonographers that perform more ultrasound scans will likely work in screening centers with high volumes, which may increase their

exposure to abnormal cases when discussing or evaluating images of patients from fellow colleagues. Secondly, as the number of ultrasound scans performed on a regular base increase, the more acquainted the sonographer will be with the normal cardiac anatomy and more likely to differentiate abnormal from normal. This acquaintance might also assure that the sonographer will question the cardiac anatomy rather than their personal technical competence.

The results from this audit enable the development of strategies to increase prenatal detection of CHDs by improving the quality of cardiac scanning, as well as recognition of abnormalities. First of all, centralization of care and thus an increase in the sonographer's annual volumes might improve the quality of cardiac scans. Due to significant implications of this intervention for screening centers, sonographers and the accessibility to health care in general, a critical assessment considering various aspects should be performed. This includes the evaluation of the feasibility and effectiveness of this intervention compared to other strategies to strengthen the performance of sonographers, as well as the perspectives of sonographers.

The incorporation of training in abnormal cases to obtain adaptational skills, rather than the evaluation of the performance of the sonographer in the normal setting could also be of additional value. Although it would be desirable to include scanning of real CHD fetuses in the sonographer's training programs, for example in a tertiary referral center, this is not feasible due to the high number of sonographers versus the emotional burden for these pregnant women. Ultrasound simulators to train both normal and pathological findings are potentially an ideal tool to teach, to improve and monitor physicians' ultrasound skills in detecting fetal anomalies. In fact, the use of ultrasound simulators was already reported 20 years ago to train fetal nuchal translucency thickness and crown-rump length measurements.[12]

The recent editioral by Yagel and Moon-Grady[4], suggests more frequent or extensive auditing of individual operators and ultrasound departments in general to enhance screening performance. In the Netherlands the sonographer's performance is already monitored every two years to remain qualified. As our data show that sonographers primarily experience difficulty in adapting to abnormal anatomy, intensifying monitoring will be of limited additional value. Therefore, time and resources should be invested in interventions with a potentially higher yield.

Strategies to enhance prenatal detection should also incorporate measures to increase exposure to abnormal anatomy and improve recognition of cardiac defects. Currently available educational platforms, such as 'Fetal Heart Academy', include fetal ultrasound

images of cardiac defects to subject sonographers to abnormal scans. It has never been studied whether the use of these platforms on a frequent basis could increase knowledge and therewith recognition of fetal heart defects. The development of a platform that enables sonographers to safely and anonymously share difficult cases with fellow sonographers or experts could be a promising tool. Operators should acquire videoclips in addition to 'still images' to not only improve scan quality, but optimize consultation by a third party in these difficult cases as well. The use of such platforms would not only increase exposure to abnormal anatomy amongst sonographers, but could lower the threshold to consult colleagues as well. This potentially results in less but more appropriate referrals to tertiary care centers, and therewith even reduce the costs of screening for CHD in general.

Heart defects that had not been recognized antenatally often involved those with a normal four-chamber view that could only be recognized in the outflow tract views. Utilizing innovative approaches such as 'automatic image recognition' through Artificial Intelligence (AI) can significantly enhance defect recognition, which may significantly improve prenatal detection of CHDs. Colleagues from the University of San Francisco already showed promising preliminary results on the use of 'automatic image recognition' in original acquired images of CHD cases and normal controls. Its applicability in prenatal screening for CHD requires further study to ensure both high sensitivity for patient detection and specificity to minimize unnecessary referrals. If future research shows that CHD detection by AI is comparable to our current golden standard, the fetal cardiology experts, this tool would be a major step forward to further improve prenatal detection rates in both Western and non-Western countries. It is however crucial to acknowledge that variations in image quality due to differences in expertise and settings can impact the overall yield and diagnostic value.

Altogether, these results suggest several potencies to improve prenatal detection for CHD.

Quality of prenatal screening can potentially be improved by enforcing a minimal annual volume or centralization of care. Inadequate adaptational skills or insufficient recognition of CHDs impedes prenatal detection in the majority of undetected cases. Interventions to potentially enhance the sonographer's performance include the use of interprofessional platforms for discussion, ultrasound training simulators, the use of automatic imaging recognition or even psychological training to cope with triggered insecurities. Future research is required to evaluate the most potent, feasible and cost-effective approach to accomplish this.

ETHICAL CONSIDERATIONS IN SCREENING FOR CHD

Screening programs intend to identify individuals in the pre-symptomatic phase of disease amongst those that appear well and did not seek medical attention yet.[13, 14] These programs aim to minimize consequences of disease through early identification and optimal treatment. The organization of a screening program, however, requires sufficient financial resources, equipment, qualified personnel and monitoring.

In 1968 the World Health Organization published a report by Wilson and Jungner describing 10 principles of screening.[15] This was later transformed into a set of 3 domains including the 12 modified criteria that should be considered before initiating a screening program.[16, 17] Following these criteria, it is impeccable that congenital heart defects meet the requirements in which screening should be concerned. First of all, CHDs have a major impact on a child's health and are known to be the most common cause of infant death and mortality from all birth defects.[18] The target population is well-defined and generally includes all first or second trimester fetuses, because the vast majority of CHD cases occur in low-risk populations. Interestingly, the main purpose of screening for congenital anomalies - as described by the 'National Institute for Public Health and the Environment' (RIVM) – merely mentions the opportunity for parents to make reproductive choices.

The second domain includes criteria for the test' performance and possibilities for intervention. Regarding the performance, screening for CHD should be accurate and acceptable. Currently, prenatal detection rates of 60-80% have been reported in a low-risk setting, after a significant increase over the past 20 years.[7, 19] Theoretically, most cardiac lesions can be detected in the fetus – with the exception of some (minor) lesions such as secundum atrial septal defect and patent ductus arteriosus. In reality, approximately 30% remains undetected before birth. While there is potential to enhance the sensitivity and specificity of screening for CHD, prenatal detection rates have significantly improved over time due to the growing expertise and increase in evidence to sustain this progress. Another aspect of screening involves the insurance that the screening test' results are clearly interpretable. The majority of studies on the prognosis of CHD however include postnatal studies, whereas evidence from a fetal perspective is limited. This impedes counselors to estimate what the clinical value of their findings are in the fetus. Therefore, evidence on the prognosis after birth is available, but suboptimal at time of a diagnosis. With regards to the opportunity for intervention, prenatal screening does allow for it, but only in selection of CHD: fetus with valvular anomalies, in whom intrauterine treatment might be favorable. Invasive

interventions in utero are, however, only performed in few fetal surgical care centers and the treatment is still considered experimental.[20, 21]

The third domain assesses the potential benefit and harm of screening. A prenatal diagnosis of CHD has evident advantages, as it provides parents prognostic information before birth, enables them to make decisions concerning their (future) family and ensures optimal perinatal care management. Unpublished data from our cohort of nearly 4000 CHD fetuses (2002-2016), indicate that despite improved prenatal detection and genetic testing for fetal CHD, the proportion of elective pregnancy terminations did not increase. Thus, prenatal detection does not seem to lower the termination threshold but enables early identification of a larger, likely less severe, portion of congenital heart defects. Timely diagnosis of fetal CHD empowers informed decisions, reducing late-term terminations and its related complications.

Referencing a comprehensive meta-analysis, prenatal diagnosis has been shown to decrease the risk of cardiovascular compromise before surgery for critical cardiac lesions.[22] Additionally, in a neonatal cohort with duct-dependent critical CHD, a notable reduction in postnatal mortality and cardiac arrest risk prior to surgery was reported, along with a decrease in preoperative ventilation and vasoactive medication.[23] For a specific subset of patients with valvular anomalies, intrauterine treatments such as aortic or pulmonary balloon valvuloplasty, or atrial needle septoplasty, may potentially enhance prognosis.[24-26] However, it is essential to emphasize that critical diagnoses significantly benefit from prenatal diagnosis, but only represent a minority (comprising less than 25% of all CHDs). Evidence supporting the favorable impact of timely diagnosis on outcomes in other congenital heart defects is scarce and often inconsistent.

The potential harm of prenatal screening has hardly been studied. A prenatal diagnosis may cause increased parental stress or anxiety levels, which can (directly or indirectly) affect the fetal health. In some cases, a prenatal diagnosis cannot be made with certainty or the prognosis is unknown. In these situations, prenatal screening induces more insecurity about the fetus' prognosis, even potentially unnecessary. On the opposite, if the heart appears structurally normal on the first or second trimester scan, this does not guarantee a structurally normal heart at birth. One of the advantages of a prenatal diagnosis is the ability for adequate perinatal management. This is mainly essential in a fetus with a critical CHD, at risk for rapid cardiac deterioration and postnatal complications after birth. The impact of postnatal complications due to delayed diagnosis and inadequate care seems relatively low from a national perspective with current detection rates. Univentricular heart defects or lesions that present with an extremely abnormal four-chamber view are detected in nearly all fetuses. Some

critical congenital heart defects, among which transposition of the aorta, aortic stenosis and aortic coarctation, are however not uncommon to be missed.

Based on my personal experience and discussions with nearly 100 mothers of both prenatally detected and undetected CHD patients, I believe that the opportunity to prepare for a child with a significant anomaly such as CHD before birth, is highly valuable to (future) parents and outweighs the potential harm. Although psychological factors of an antenatal miss or prenatal diagnosis were not officially studied, many parents motivated the reason for their consent to participate spontaneously during follow-up (concerning the study 'Why are congenital heart defects being missed?', Chapter 2). Frequently, mothers of undetected cases mentioned to aspire the prevention of a missed diagnoses in similar cases in the future. This would potentially prevent cardiac deterioration in other children and timely prepare parents for having a child with CHD. Only a small proportion of mothers reported to be grateful that the diagnosis remained undetected before birth, as they enjoyed a carefree pregnancy and did not experience any negative effect of a delayed diagnosis for their child. It would be interesting to further assess the psychological effects of a missed diagnosis and false parental reassurance following prenatal screening. Especially for undetected critical CHD cases, as this has – to my knowledge – never been thoroughly studied so far.

In the Netherlands, the 'National Institute for Public Health and the Environment' (RIVM) is responsible for the management and provision of information regarding population screening programs. It also serves as an advisory body, providing information to policymakers in the country. Their formal report on prenatal screening (named 'Prenatal screening', published 2016), intended for the Dutch Health Council, solely describes prenatal screening as a measure to provide 'reproductive choices'. This emphasizes only a limited aspect of the motivation to screen for congenital anomalies. Given their mandate to consolidate knowledge, facilitate innovation in population screening when deemed necessary, and provide recommendations to policymakers, it is important that such institutes consider all aspects of screening, as advocated by the WHO in 1968.

In conclusion, fetuses with a prenatal diagnosis of a critical (duct-dependent) CHD benefit from a timely diagnosis and optimal perinatal care management. Yet, scientifically proving this for all structural cardiac anomalies remains challenging. This can be ascribed to the low prevalence of specific heart defects and the considerably lower detection rates, especially for non-critical CHDs, up to a decade ago. Based on numerous parental declarations, the opportunity to prepare for a child with a CHD before birth is highly valuable and outweighs the potential harm in my opinion. With increasing detection rates and subsequent options for genetic testing, potentially

negative effects of prenatal screening should be critically evaluated as well. Future research is needed in order to organize health care according to evidence-based best practices, and with respect to the benefits of timely diagnosis and the potential harm of screening.

FUTURE PERSPECTIVES

It is imperative to acquire evidence concerning the entire developmental journey and outcome, beginning as early as the fetal stage, to optimize care for children with CHD. Due to the rarity of cardiac defects and rapid innovations in this field, financial support is essential to develop and sustain a large national CHD registry. This registry would allow future studies to collection essential data and monitor the national screening performance.

First of all, optimal fetal and neonatal care requires early identification of cases, preferably in the fetus. Future research should evaluate the effectiveness of new strategies to improve prenatal detection for CHD, such as training in abnormal cases or psychological interventions to optimize referrals to specialized fetal echo facilities. Additionally, the use of artificial intelligence should be studied, as this may aid sonographers in the recognition of fetal cardiac abnormalities, both in Western and non-Western areas worldwide.

Secondly, counseling following a prenatal diagnosis demands sufficient evidence from a fetal perspective to enhance fetal and perinatal care management. Future studies should therefore always relate evidence regarding prognosis to the time of diagnosis. Lastly, with the rapidly evolving techniques and possibilities for genetic testing, parents should already be counseled on the impact of (additional) genetic diagnoses in an early stage and beyond the scope of pregnancy termination. Besides that, future research should aim to find a balance between optimizing fast and complete genetic testing for all variants, limiting the potentially negative consequences and potentially develop functional tests to aid the translation of these genetic results to their phenotypical consequences.

REFERENCES

1. Aliasi M, Snoep MC, van Geloven N, Haak MC. Birthweight and isolated congenital heart defects - A systematic review and meta-analysis. BJOG. 2022;129(11):1805-16.
2. Snoep MC, Aliasi M, van der Meeren LE, Jongbloed MRM, DeRuiter MC, Haak MC. Placenta morphology and biomarkers in pregnancies with congenital heart disease - A systematic review. Placenta. 2021;112:189-96.
3. Pels A, Beune IM, van Wassenaer-Leemhuis AG, Limpens J, Ganzevoort W. Early-onset fetal growth restriction: A systematic review on mortality and morbidity. Acta Obstet Gynecol Scand. 2020;99(2):153-66.
4. Yagel S, Moon-Grady AJ. Fetal cardiac evaluation services for low-risk pregnancies: how can we improve? Ultrasound Obstet Gynecol. 2020;55(6):726-7.
5. Bak GS, Shaffer BL, Madriago E, Allen A, Kelly B, Caughey AB, et al. Detection of fetal cardiac anomalies: cost-effectiveness of increased number of cardiac views. Ultrasound Obstet Gynecol. 2020;55(6):758-67.
6. van Velzen CL, Clur SA, Rijlaarsdam ME, Pajkrt E, Bax CJ, Hruda J, et al. Prenatal diagnosis of congenital heart defects: accuracy and discrepancies in a multicenter cohort. Ultrasound Obstet Gynecol. 2016;47(5):616-22.
7. van Velzen CL, Clur SA, Rijlaarsdam ME, Bax CJ, Pajkrt E, Heymans MW, et al. Prenatal detection of congenital heart disease--results of a national screening programme. BJOG. 2016;123(3):400-7.
8. International Society of Ultrasound in O, Gynecology, Carvalho JS, Allan LD, Chaoui R, Copel JA, et al. ISUOG Practice Guidelines (updated): sonographic screening examination of the fetal heart. Ultrasound Obstet Gynecol. 2013;41(3):348-59.
9. Donofrio MT, Moon-Grady AJ, Hornberger LK, Copel JA, Sklansky MS, Abuhamad A, et al. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. Circulation. 2014;129(21):2183-242.
10. AIUM Practice Parameter for the Performance of Fetal Echocardiography. J Ultrasound Med. 2020;39(1):E5-E16.
11. Lee W, Allan L, Carvalho JS, Chaoui R, Copel J, Devore G, et al. ISUOG consensus statement: what constitutes a fetal echocardiogram? Ultrasound Obstet Gynecol. 2008;32(2):239-42.
12. Maul H, Scharf A, Baier P, Wustemann M, Gunter HH, Gebauer G, et al. Ultrasound simulators: experience with the SonoTrainer and comparative review of other training systems. Ultrasound Obstet Gynecol. 2004;24(5):581-5.
13. Zavon MR. Principles and Practice of Screening for Disease. Archives of Internal Medicine. 1969;123(3):349-.
14. Wald NJ. Guidance on terminology. J Med Screen. 2006;13(1):53.
15. Wilson JM, Jungner YG. [Principles and practice of mass screening for disease]. Bol Oficina Sanit Panam. 1968;65(4):281-393.
16. Andermann A, Blancquaert I, Beauchamp S, Dery V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. Bull World Health Organ. 2008;86(4):317-9.
17. Dobrow MJ, Hagens V, Chafe R, Sullivan T, Rabeneck L. Consolidated principles for screening based on a systematic review and consensus process. CMAJ. 2018;190(14):E422-E9.

18. Wang Y, Liu G, Canfield MA, Mai CT, Gilboa SM, Meyer RE, et al. Racial/ethnic differences in survival of United States children with birth defects: a population-based study. J Pediatr. 2015;166(4):819-26 e1-2.
19. Everwijn SMP, van Nisselrooij AEL, Rozendaal L, Clur SB, Pajkrt E, Hruda J, et al. The effect of the introduction of the three-vessel view on the detection rate of transposition of the great arteries and tetralogy of Fallot. Prenat Diagn. 2018;38(12):951-7.
20. Araujo Junior E, Tonni G, Chung M, Ruano R, Martins WP. Perinatal outcomes and intrauterine complications following fetal intervention for congenital heart disease: systematic review and meta-analysis of observational studies. Ultrasound Obstet Gynecol. 2016;48(4):426-33.
21. Moon-Grady AJ. Re: Perinatal outcomes and intrauterine complications following fetal intervention for congenital heart disease: systematic review and meta-analysis of observational studies. E. Araujo Junior, G. Tonni, M. Chung, R. Ruano and W. P. Martins. Ultrasound Obstet Gynecol 2016; 48: 426-433. Ultrasound Obstet Gynecol. 2016;48(4):424-5.
22. Holland BJ, Myers JA, Woods CR, Jr. Prenatal diagnosis of critical congenital heart disease reduces risk of death from cardiovascular compromise prior to planned neonatal cardiac surgery: a meta-analysis. Ultrasound Obstet Gynecol. 2015;45(6):631-8.
23. Thakur V, Dutil N, Schwartz SM, Jaeggi E. Impact of prenatal diagnosis on the management and early outcome of critical duct-dependent cardiac lesions. Cardiol Young. 2018;28(4):548-53.
24. Freud LR, McElhinney DB, Marshall AC, Marx GR, Friedman KG, del Nido PJ, et al. Fetal aortic valvuloplasty for evolving hypoplastic left heart syndrome: postnatal outcomes of the first 100 patients. Circulation. 2014;130(8):638-45.
25. Friedman KG, Sleeper LA, Freud LR, Marshall AC, Godfrey ME, Drogosz M, et al. Improved technical success, postnatal outcome and refined predictors of outcome for fetal aortic valvuloplasty. Ultrasound Obstet Gynecol. 2018;52(2):212-20.
26. Marshall AC, van der Velde ME, Tworetzky W, Gomez CA, Wilkins-Haug L, Benson CB, et al. Creation of an atrial septal defect in utero for fetuses with hypoplastic left heart syndrome and intact or highly restrictive atrial septum. Circulation. 2004;110(3):253-8.