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Congenital heart defects: from a prenatal perspective

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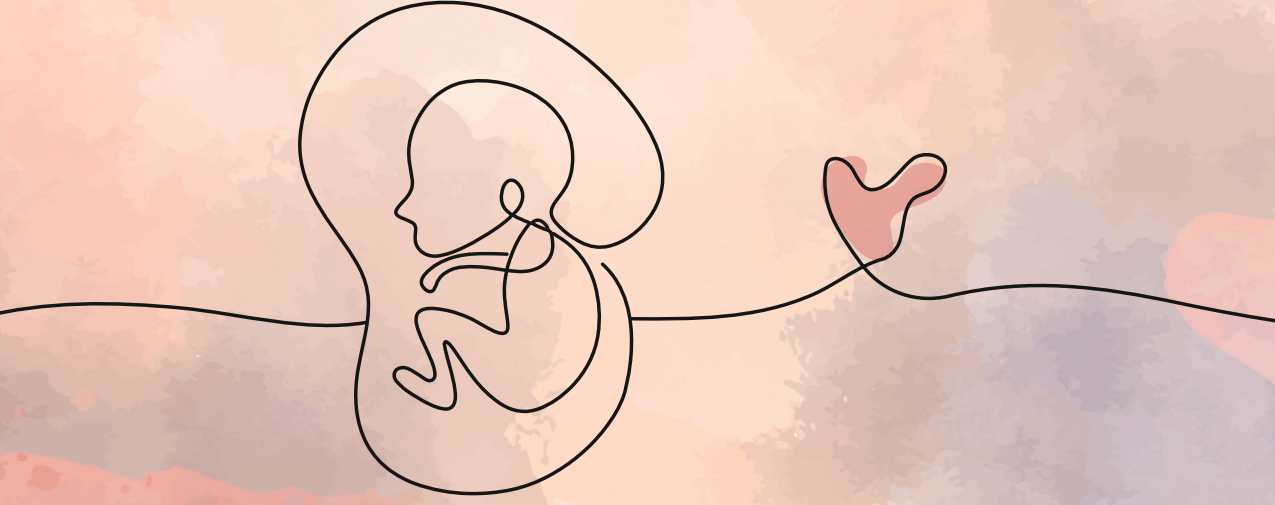
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CHAPTER 1

General introduction

Congenital heart defects (CHD) are the most common congenital defect with a prevalence of 6-10 per 1 000 newborns.¹ These concern a severe heart defect in 2-3 per 1 000 newborns, which is defined as the need for surgery or an intervention within the first year of life.² The clinical presentation of (severe) congenital heart defects can vary significantly between diagnoses. Timely recognition of CHD is therefore warranted to prevent potentially life-threatening situations or permanent damage, as CHD remain one of the leading causes of congenital defect-related infant morbidity and mortality.³ The majority of infant deaths attributable to CHD occur within the first 28 days after birth (also known as the neonatal period).⁴

One of the major changes in the transition from fetal to neonatal circulation is the closure of the ductus arteriosus, which generally closes within 72 hours after birth.⁵ Neonates with a ductal-dependent CHD, however, rely upon a patent ductus arteriosus (PDA) to enable sufficient blood supply to the pulmonary or systemic circulation or allow adequate mixing between parallel circulations. Prostaglandin administration directly after birth can prevent acute cardiac decompensation in these patients and bridge the time until surgery is feasible.⁶

The majority of critical CHD neonates are symptomatic and therefore identified soon after birth. However, up to 30% of critical CHD neonates appear normal on routine examination and may be discharged home without diagnosis.^{7,8} The mortality risk in critical CHD neonates that remain unidentified during birth hospitalization, is reported to be as high as 30%.⁹ If the time to diagnosis and referral to a tertiary care center with expertise and optimal neonatal care is longer, the morbidity and mortality risk in these cases has proven to increase as well.^{9,10} Timing of clinical manifestation may vary significantly between critical cardiac defects. Especially cardiac defects that do not depend upon a patent ductus arteriosus are unlikely to become symptomatic within the first 72 hours, yet a delayed diagnosis can result in similarly poor outcomes. Besides that, cyanosis is often not clinically recognized in mild desaturation (>80% saturation), anemia or darkly pigmented infants. Most developed countries therefore implemented the use of pulse oximetry as a routine screening tool in asymptomatic newborns to improve recognition of (cyanotic) cardiac defects after birth.^{11,12}

Antenatal screening for CHD

Following the first paper on the use of sonography in obstetrics in 1958¹³, ultrasound has become an essential tool to visualize fetal (cardiac) anatomy with great detail and diagnose structural anomalies as soon as mid-gestation. A prenatal diagnosis enables a planned delivery in a neonatal care facility with prompt and optimal treatment, and therewith reduce mortality and improve long-term outcome as described above.¹⁴⁻¹⁹

Furthermore, prenatal diagnosis allows for further monitoring and the opportunity to perform genetic analyses to optimize prenatal counseling and prepare parents for having a child with CHD. In severe cases, this may even lead to the parent's decision to opt for termination of pregnancy.

Only 10% of all fetuses with a cardiac defect occur in pregnancies with known risk factors to develop CHD. On the other hand, 90% of fetuses with CHD are encountered unexpectedly in otherwise healthy families.^{20,21} Therefore, most developed countries have set up population-based screening programs to optimize fetal detection rates for congenital heart defects. Although these programs vary between and even within countries, the majority offer a routine anomaly scan for all pregnant women around 20 weeks of gestation, regularly preceded by a first trimester anomaly scan to detect major congenital anomalies. Practice guidelines for sonographic screening at mid-gestation recommend diagnostic imaging of the 'four-chamber view' as well as the different outflow tract views. This systematic approach aids to identify fetuses at risk for structural anomalies in a low-risk setting, to maximize the detection of cardiac anomalies during a second-trimester scan.²²⁻²⁴

The structural anomaly scan (SAS) was introduced as part of the national screening program for congenital anomalies in the Netherlands in 2007. The Dutch screening program has a unique character, due to the fact that its training program and quality monitoring is regulated on a national level. All sonographers operate following a standardized scanning protocol and are certified after uniform training requisites. Eight regional centers therewith monitor the quality of the ultrasound images for all sonographers, as well as the minimum scans that should be performed by each sonographer on a yearly basis, in order for them to stay qualified.^{25,26}

Despite standardized guidelines and protocols, structural cardiac anomalies remain the most frequently missed congenital defect on fetal ultrasound.²⁷ Screening programs have reported detection rates between 30–75% in most developed countries.²⁸⁻³⁴ Single-center studies, on the other hand, achieve detection rates up to 80–90%.³⁵⁻³⁷ Heart defects that present with a normal four-chamber view appear the most likely to be missed, especially in the absence of known risk factors or additional structural anomalies.^{26,38,39} Although never studied in current literature, it is commonly thought that these discrepancies in detection rates rely on differences in (modifiable) factors, such as examiner experience, maternal obesity, gestational age and fetal position. If modifiable factors that impede prenatal detection can be identified, the sensitivity of national or regional screening programs may potentially increase to the 80–90%, as reported in single-center studies.

Prenatal counseling

One of the advantages of a prenatal diagnosis is the ability to inform and counsel parents before birth. It is essential for counseling that the prenatal diagnosis is accurate, ideally with an evidence-based estimate of the prognosis. This information is crucial for optimal postnatal care management, as well as informed decision making in case parents consider pregnancy termination.

Currently available literature, however, often focuses on the prognosis of neonates with a certain CHD following (successful) surgical correction or intervention.^{3,40} Fetuses diagnosed with a CHD comprise a significantly different population, as those that demise before birth or do not make it to surgery are not included. To improve prenatal counseling at mid-gestation, fetal studies that report on the prognosis of these cardiac diagnoses from a fetal perspective are needed to facilitate reliable and patient-centered estimates of pre- and postnatal outcome.

Congenital heart defects are associated with additional extracardiac anomalies, neurodevelopmental delay and chromosome or genetic alterations.⁴¹⁻⁴⁴ These co-morbidities may have a significant impact on the prognosis as well. After initial recognition that the heart is abnormal on fetal ultrasound, an advanced ultrasound examination by a fetal echocardiography expert is performed, to ascertain the diagnosis and assess the presence of other structural anomalies. A prenatal diagnosis also enables further genetic testing to timely identify genetic alterations in the fetal DNA, as CHD have been described as part of many genetic syndromes. Thus far, only a few cohort studies have reported the estimated incidence of genetic diagnoses in fetuses diagnosed with a CHD. Many of these studies are somewhat outdated, as they mainly focus on numerical chromosome abnormalities, such as trisomies or triploidy, or 22q11.2 deletion syndrome specifically.⁴⁵⁻⁴⁷ Recently, innovative techniques including microarray analysis and exome sequencing allow to diagnose other copy number variations or genetic mutations as well. As chromosomal and genetic alterations can have a major impact on (neuro-)development, quality of life and life expectancy of children with a CHD, most developed countries already offer microarray analysis as the standard of care in the fetal setting to identify copy number variations.⁴⁸ The use of targeted or whole-exome sequencing to detect subtle genetic variations, commonly referred to as 'genetic mutations', is often preserved for a minority of CHD cases. Population-based studies that evaluate the direct relation between specific cardiac defects and the prevalence of genetic syndromes to this extend, have hardly been published in current literature. Evidence on the prevalence of these genetic variants can improve prenatal counseling in cases with severe CHD and aid professionals to decide whether the use of currently available additional tests, such as exome sequencing (ES) or genetic testing for specific genetic syndromes is indicated.

AIMS AND OUTLINE OF THIS THESIS

The aim of this thesis is to study factors that influence the potential to detect congenital heart defects before birth and gather knowledge on the prognosis of antenatally detected cases with a congenital heart defect in order to improve prenatal counseling and postnatal care management.

Prenatal detection

This part of this theses aims to evaluate the influence of risk factors and identify causes for a missed prenatal diagnosis at mid-gestation to improve prenatal detection rates for congenital heart defects. The results of our case-control study are presented in **chapter 2**, where we describe differences in baseline characteristics, sonographer's experience and quality of ultrasound exams between prenatally undetected and detected cases with a congenital heart defect.

Outcome

The second part of this thesis focuses on the prognosis of congenital heart defects following a prenatal diagnosis at mid-gestation. In **chapter 3** we explored the prevalence of genetic diagnoses in the majority of congenital heart defects, either isolated or non-isolated, and evaluated the impact of these diagnoses on mortality and morbidity. As suggested in a Letter to the Editor, we additionally report the proportion of genetic diagnoses that is detectable with either chromosome microarray analysis (CMA) and exome sequencing for each congenital heart defect separately in **chapter 4**, to aid clinicians determine the genetic tests that should be performed.

Neurodevelopmental delay is frequently encountered in children with congenital heart defects. In **chapter 5**, we report on a cohort study evaluating the impact of extracardiac pathology on fetal head circumference - as a marker for brain development - to identify whether delayed neurodevelopment can be purely attributed to hemodynamic changes in utero caused by these heart defects.

The final chapters of this thesis focus on prenatal diagnoses that are challenging to counsel at mid-gestation, due to limited evidence on the outcome of these particular findings from a prenatal perspective. Ventricular size disproportion - for example - is a marker for aortic coarctation (CoA) in fetal life. Approximately 50% of these fetuses do, however, not develop CoA after birth. In **chapter 6**, we evaluate the postnatal outcome of cases with ventricular disproportion in the absence of CoA in a cohort of prenatally detected cases. **Chapter 7** describes a cohort study and systematic literature review on the outcome of fetal common arterial trunk beyond the neonatal period and

Chapter 1

with regard to the presence of genetic diagnoses, extracardiac malformations and neurodevelopment. In **chapter 8**, we report on an international retrospective case series and systematic literature review to provide information on the outcome of fetuses with aorto-left ventricular tunnel, a diagnosis that is rarely made before birth.

REFERENCES

1. van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2011;58(21):2241-7.
2. Leirgul E, Fomina T, Brodwall K, Greve G, Holmstrom H, Vollset SE, et al. Birth prevalence of congenital heart defects in Norway 1994-2009--a nationwide study. *Am Heart J*. 2014;168(6):956-64.
3. Oster ME, Lee KA, Honein MA, Riehle-Colarusso T, Shin M, Correa A. Temporal trends in survival among infants with critical congenital heart defects. *Pediatrics*. 2013;131(5):e1502-8.
4. Pierpont ME, Basson CT, Benson DW, Jr., Gelb BD, Giglia TM, Goldmuntz E, et al. Genetic basis for congenital heart defects: current knowledge: a scientific statement from the American Heart Association Congenital Cardiac Defects Committee, Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. *Circulation*. 2007;115(23):3015-38.
5. Dice JE, Bhatia J. Patent ductus arteriosus: an overview. *J Pediatr Pharmacol Ther*. 2007;12(3):138-46.
6. Akkinapally S, Hundalani SG, Kulkarni M, Fernandes CJ, Cabrera AG, Shivanna B, et al. Prostaglandin E1 for maintaining ductal patency in neonates with ductal-dependent cardiac lesions. *Cochrane Database Syst Rev*. 2018;2:CD011417.
7. Khoshnood B, Lelong N, Houyel L, Thieulin AC, Jouannic JM, Magnier S, et al. Prevalence, timing of diagnosis and mortality of newborns with congenital heart defects: a population-based study. *Heart*. 2012;98(22):1667-73.
8. Ailes EC, Gilboa SM, Honein MA, Oster ME. Estimated number of infants detected and missed by critical congenital heart defect screening. *Pediatrics*. 2015;135(6):1000-8.
9. Eckersley L, Sadler L, Parry E, Finucane K, Gentles TL. Timing of diagnosis affects mortality in critical congenital heart disease. *Arch Dis Child*. 2016;101(6):516-20.
10. de-Wahl Granelli A, Wennergren M, Sandberg K, Mellander M, Bejlum C, Inganas L, et al. Impact of pulse oximetry screening on the detection of duct dependent congenital heart disease: a Swedish prospective screening study in 39,821 newborns. *BMJ*. 2009;338:a3037.
11. Narayan IC, Blom NA, Ewer AK, Vento M, Manzoni P, te Pas AB. Aspects of pulse oximetry screening for critical congenital heart defects: when, how and why? *Arch Dis Child Fetal Neonatal Ed*. 2016;101(2):F162-7.
12. Plana MN, Zamora J, Suresh G, Fernandez-Pineda L, Thangaratnam S, Ewer AK. Pulse oximetry screening for critical congenital heart defects. *Cochrane Database Syst Rev*. 2018;3:CD011912.
13. Donald I, Macvicar J, Brown TG. Investigation of abdominal masses by pulsed ultrasound. *Lancet*. 1958;1(7032):1188-95.
14. Calderon J, Angeard N, Moutier S, Plumet MH, Jambaque I, Bonnet D. Impact of prenatal diagnosis on neurocognitive outcomes in children with transposition of the great arteries. *J Pediatr*. 2012;161(1):94-8 e1.
15. Chakraborty A, Gorla SR, Swaminathan S. Impact of prenatal diagnosis of complex congenital heart disease on neonatal and infant morbidity and mortality. *Prenat Diagn*. 2018;38(12):958-63.

16. Franklin O, Burch M, Manning N, Sleeman K, Gould S, Archer N. Prenatal diagnosis of coarctation of the aorta improves survival and reduces morbidity. *Heart*. 2002;87(1):67-9.
17. Peyvandi S, De Santiago V, Chakkarapani E, Chau V, Campbell A, Poskitt KJ, et al. Association of Prenatal Diagnosis of Critical Congenital Heart Disease With Postnatal Brain Development and the Risk of Brain Injury. *JAMA Pediatr*. 2016;170(4):e154450.
18. Quartermain MD, Hill KD, Goldberg DJ, Jacobs JP, Jacobs ML, Pasquali SK, et al. Prenatal Diagnosis Influences Preoperative Status in Neonates with Congenital Heart Disease: An Analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database. *Pediatr Cardiol*. 2019;40(3):489-96.
19. 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.
20. Allan L. Antenatal diagnosis of heart disease. *Heart*. 2000;83(3):367.
21. Sharland G. Fetal cardiac screening and variation in prenatal detection rates of congenital heart disease: why bother with screening at all? *Future Cardiol*. 2012;8(2):189-202.
22. Carvalho JS, Mavrides E, Shinebourne EA, Campbell S, Thilaganathan B. Improving the effectiveness of routine prenatal screening for major congenital heart defects. *Heart*. 2002;88(4):387-91.
23. Everwijn SMP, van Nisselrooij AEL, Rozendaal L, Clur SB, Pajkrt E, Hruđa 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.
24. Viñals F, Heredia F, Giuliano A. The role of the three vessels and trachea view (3VT) in the diagnosis of congenital heart defects. *Ultrasound Obstet Gynecol*. 2003;22(4):358-67.
25. Gijtenbeek M, Haak MC. [The standard mid-pregnancy anomaly scan in the Netherlands: what is its effect?]. *Ned Tijdschr Geneesk*. 2017;161:D1293.
26. 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.
27. 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.
28. Galindo A, Herraiz I, Escribano D, Lora D, Melchor JC, de la Cruz J. Prenatal detection of congenital heart defects: a survey on clinical practice in Spain. *Fetal Diagn Ther*. 2011;29(4):287-95.
29. Levy DJ, Pretorius DH, Rothman A, Gonzales M, Rao C, Nunes ME, et al. Improved prenatal detection of congenital heart disease in an integrated health care system. *Pediatr Cardiol*. 2013;34(3):670-9.
30. Lytzen R, Vejlstrop N, Bjerre J, Petersen OB, Leenskjold S, Dodd JK, et al. Live-Born Major Congenital Heart Disease in Denmark: Incidence, Detection Rate, and Termination of Pregnancy Rate From 1996 to 2013. *JAMA Cardiol*. 2018;3(9):829-37.
31. Marek J, Tomek V, Skovránek J, Povysilová V, Samánek M. Prenatal ultrasound screening of congenital heart disease in an unselected national population: a 21-year experience. *Heart*. 2011;97(2):124-30.
32. Sharland GK, Allan LD. Screening for congenital heart disease prenatally. Results of a 2 1/2-year study in the South East Thames Region. *Br J Obstet Gynaecol*. 1992;99(3):220-5.

33. Khoo NS, Van Essen P, Richardson M, Robertson T. Effectiveness of prenatal diagnosis of congenital heart defects in South Australia: a population analysis 1999-2003. *Aust N Z J Obstet Gynaecol.* 2008;48(6):559-63.
34. Stümpflen I, Stümpflen A, Wimmer M, Bernaschek G. Effect of detailed fetal echocardiography as part of routine prenatal ultrasonographic screening on detection of congenital heart disease. *Lancet.* 1996;348(9031):854-7.
35. Cuneo BF, Curran LF, Davis N, Elrad H. Trends in prenatal diagnosis of critical cardiac defects in an integrated obstetric and pediatric cardiac imaging center. *J Perinatol.* 2004;24(11):674-8.
36. Clur SA, Van Brussel PM, Ottenkamp J, Bilardo CM. Prenatal diagnosis of cardiac defects: accuracy and benefit. *Prenat Diagn.* 2012;32(5):450-5.
37. Letourneau KM, Horne D, Soni RN, McDonald KR, Karlicki FC, Fransoo RR. Advancing Prenatal Detection of Congenital Heart Disease: A Novel Screening Protocol Improves Early Diagnosis of Complex Congenital Heart Disease. *J Ultrasound Med.* 2018;37(5):1073-9.
38. Wong SF, Chan FY, Cincotta RB, Lee-Tannock A, Ward C. Factors influencing the prenatal detection of structural congenital heart diseases. *Ultrasound Obstet Gynecol.* 2003;21(1):19-25.
39. Acherman RJ, Evans WN, Luna CF, Rollins R, Kip KT, Collazos JC, et al. Prenatal detection of congenital heart disease in southern Nevada: the need for universal fetal cardiac evaluation. *J Ultrasound Med.* 2007;26(12):1715-9; quiz 20-1.
40. Verheugt CL, Uiterwaal CS, Grobbee DE, Mulder BJ. Long-term prognosis of congenital heart defects: a systematic review. *Int J Cardiol.* 2008;131(1):25-32.
41. de Wit MC, Srebniak MI, Govaerts LC, Van Opstal D, Galjaard RJ, Go AT. Additional value of prenatal genomic array testing in fetuses with isolated structural ultrasound abnormalities and a normal karyotype: a systematic review of the literature. *Ultrasound Obstet Gynecol.* 2014;43(2):139-46.
42. Simmons MA, Brueckner M. The genetics of congenital heart disease... understanding and improving long-term outcomes in congenital heart disease: a review for the general cardiologist and primary care physician. *Curr Opin Pediatr.* 2017;29(5):520-8.
43. Song MS, Hu A, Dyamenahalli U, Chitayat D, Winsor EJ, Ryan G, et al. Extracardiac lesions and chromosomal abnormalities associated with major fetal heart defects: comparison of intrauterine, postnatal and postmortem diagnoses. *Ultrasound Obstet Gynecol.* 2009;33(5):552-9.
44. Zaidi S, Brueckner M. Genetics and Genomics of Congenital Heart Disease. *Circ Res.* 2017;120(6):923-40.
45. Copel JA, Cullen M, Green JJ, Mahoney MJ, Hobbins JC, Kleinman CS. The frequency of aneuploidy in prenatally diagnosed congenital heart disease: an indication for fetal karyotyping. *Am J Obstet Gynecol.* 1988;158(2):409-13.
46. Paladini D, Calabro R, Palmieri S, D'Andrea T. Prenatal diagnosis of congenital heart disease and fetal karyotyping. *Obstet Gynecol.* 1993;81(5 (Pt 1)):679-82.
47. Wimalasundera RC, Gardiner HM. Congenital heart disease and aneuploidy. *Prenat Diagn.* 2004;24(13):1116-22.
48. Committee on G, the Society for Maternal-Fetal M. Committee Opinion No.682: Microarrays and Next-Generation Sequencing Technology: The Use of Advanced Genetic Diagnostic Tools in Obstetrics and Gynecology. *Obstet Gynecol.* 2016;128(6):e262-e8.