Imaging the prenatal brain in congenital heart defects

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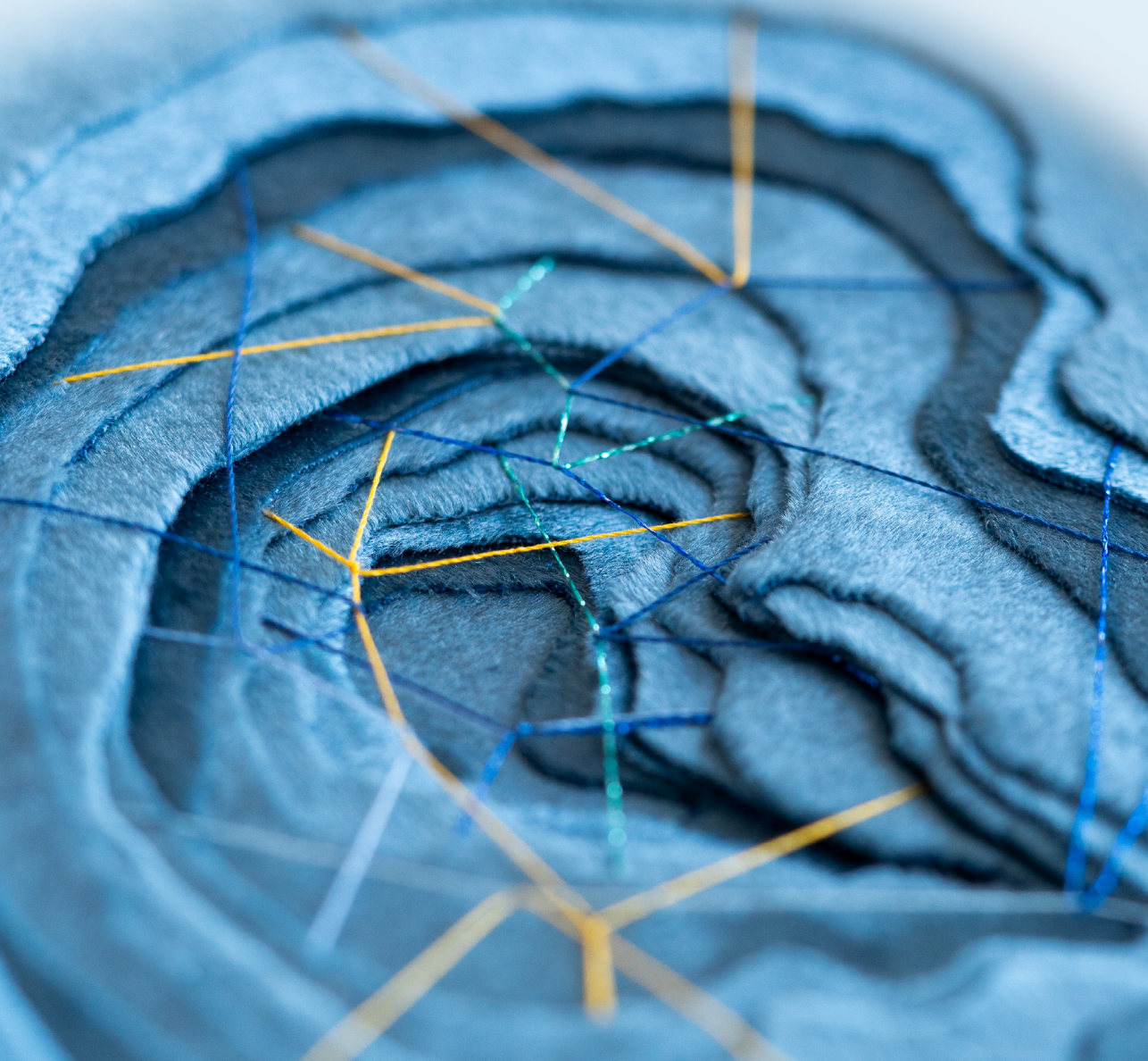
CHAPTER

9

Summary



SUMMARY

Children affected by congenital heart defects (CHD), are nowadays known to live longer and with less morbidity than children with CHD that were born some decades ago, due to the advances in perinatal, perioperative and intensive care. Long-term follow-up studies of children born with (isolated) CHD however show a high prevalence of morbidity, especially neurodevelopmental impairment. These impairments include neurologic, cognitive and behavioral deficits. In **chapter 1,** the introduction of this thesis, this topic is discussed in greater detail.

Detecting CHD antenatally has a positive effect on survival and long-term neurodevelopmental outcome in isolated CHD. Efforts that are made to increase prenatal detection of CHD are therefore of the utmost importance. Historically, CHDs that present with an abnormal four chamber-view on ultrasound, have better prenatal detection rates than CHDs that have a normal four-chamber view. The latter CHDs may present with abnormal views of the outflow tracts, which a far more difficult to recognize. **Part one, chapter 2** of this thesis shows the comparison of the prenatal detection of transposition of the great arteries (TGA) and Tetralogy of Fallot (ToF) which usually have a normal four chamber view. The detection of these two CHD-types was compared between two time periods: before and after the introduction of the three vessel view. The addition of this plane as a mandatory item in the Dutch screening protocol for the 20 weeks anomaly scan resulted in an increase of the detection of TGA from 44% to 82%, and the detection of ToF from 43% to 67%.

To explore the impact of a prenatal diagnosis on mortality rates between detected and undetected cases, we studied mortality rates of neonates with TGA within the Amsterdam-Leiden geographic region, between 2007 and 2015. Assuming that these neonates would have received immediate postnatal care, at least 4 of 9 deaths might have been prevented if they were detected prenatally. This also highlights the importance of a prenatal diagnosis to decrease mortality in TGA cases.

In **part two** of this thesis, prenatal neurodevelopment in CHD cases is studied. Chapter 3 presents a systematic review and meta-analysis of studies on this subject published before November 2015. This review showed that fetuses with CHD consistently show significantly smaller head circumferences as compared to controls across all studies; either measured by MRI, ultrasound or postnatally. The maturation of the brain was mainly studied by MRI, in which signs of delay were encountered in several studies. The studies that were included in this systematic review however, showed several methodological weaknesses such as selection bias (only the most severe end

of the CHD spectrum was studied), the absence of comparing the results with the actual outcome after birth and the inclusion of fetuses without information about the presence of a genetic syndrome. Furthermore, structural brain malformations were attributed to acquired injury, due to hemodynamic changes during pregnancy, although that actual correlation was not studied.

To explore prenatal neurodevelopment in CHD cases without the encountered weaknesses of the described studies, the HAND (Heart And Neurodevelopment) study was started in 2014. It explores cerebral development in cases with isolated congenital heart defects. All consecutive cases that are referred to our tertiary center, Leiden University Medical Center, are studied by neurosonography every 4 weeks until delivery. Since the HAND-study includes only isolated CHD cases, fetuses with known and suspected genetic malformations are not included, or excluded if a genetic syndrome became apparent after birth. The infants were followed up until the age of one year. In the neurosonography examinations, the cortical development was assessed in 2D and 3D imaging. These data resulted in the following chapters.

In **chapter 4,** we assessed the feasibility of neurosonography in a clinical setting, which means that the examinations were performed in a limited time frame. Both fetuses with a CHD as well as normal fetuses were examined. The visibility of different brain structures was scored by researchers, blinded for the presence or absence of a CHD. Intra-observer and interobserver variation turned out to be excellent. A neurosonographic examination was considered complete when at least 7/9 analysed brain structures were visible in the recorded images and clips. In the CHD group this was encountered in 79% of examinations, and in the control group in 90% of the examinations. In both groups, the examinations that were conducted between 22-34 weeks yielded the highest results, this time frame is thus considered as the optimal time for neurosonography. Also, the structures that are visible in the axial plane (lateral ventricle, cerebellum and cavum septum pellucidum), and the coronal plane (frontal horns) were visible in almost all examinations. The influence of confounding factors on visibility of cerebral structures was also considered. We found no differences in common factors that could have influenced visibility, such as mothers with BMI higher that 30, non-cephalic presenting fetuses, and non-anterior placenta's. Thus, this study showed that neurosonography for the purpose of surveillance in a clinical setting is possible, but when there is an indication for extended neurosonography and the need to see every structure of the brain, larger time-slots than then the 30 minutes that were used should be planned. Extended neurosonography with a (seemingly) unlimited time-frame, in which there is time to await a favorable fetal position, is not a realistic representation of day-to-day practice.

The cortical development in CHD-cases and controls assessed by 2D ultrasound during pregnancy is studied in **chapter 5.** Nine different brain sulci (Sylvian, parieto-occipital, central, calcarine and cingulate fissures) and brain areas (frontal, parietal, occipital and temporal areas) were scored using a chart with a range from 0 (no cortical maturation) until 5 (end-stage maturation). Of the analysed cortical structures, only the cingulate fissure and the Sylvian fissure were significantly delayed in CHD fetuses compared to controls. Alterations in these fissures are also encountered in children presenting with behavioral problems, for example in attention deficit disorder. Possibly the delays in cortical development that were found in this study could be a first expression of altered neurodevelopment in children with CHD. The differences that were found in this study were however very subtle (-0.25 grade point per fissure), which raised uncertainty about the clinical significance of this finding. On the other hand, small deviations from normal development in very early life may lead to large differences in later life, as certain developmental milestones might be missed and lead to larger developmental delays.

For the analyses in **chapter 6** and **7** a deep learning software algorithm was applied to the 3D brain volumes acquired by ultrasound, to assess the cortical age. Cortical age was plotted against true gestational age in CHD-cases and controls, to represent the speed of maturation. And thus, cortical or brain age was used as a proxy for brain development. The use of a deep-learning algorithm to analyse cortical development is superior to manual analysis, since the algorithm is trained with a large dataset of normally developed brains. The algorithm displays exactly which areas represent cortical development at every stage of prenatal development for which it was trained. Theoretically, the algorithm determines the cortical development more accurate, compared to manually selected and scored cortical fissures and areas.

In **chapter 6,** a group of 90 isolated CHD-fetuses and 75 controls were sequentially scanned and the brain-age was calculated using the aforementioned algorithm. This article represents the first clinical application of the presented algorithm. The main finding was a significant but small delay of 3 days in CHD-fetuses compared to control fetuses. This delay was consistent throughout pregnancy, defying previous reports on further deteriorating delay in cortical maturation with advancing gestational age. Again, the small delay in brain-age that was found in this study may represent a clinical significant delay in cortical development that might have a profound effect in later life. It is, however, also plausible that other factors that occur later in life play a role in neurodevelopmental delay in CHD children.

To address the influence of flow and oxygenation toward the brain in different types of CHD, a subgroup analysis is presented in **chapter 7.** A total of 660 US examinations that were performed in 142 CHD-cases and 75 controls were analysed using the brain-age algorithm. In the two subgroups, that contain TGA-cases and intracardiac mixing cases (e.g. Tetralogy of Fallot and AVSD), a significant delay of maximum 4 days compared to controls was found. Whether these findings could only be attributed to the altered cerebral oxygenation because of the cardiac lesion, remains uncertain. A great number of factors play a role in the etiology of neurodevelopmental delay in CHD-children, some of which might not be known yet.

Lastly, in **chapter 8,** all the findings in this thesis are discussed, and recommendations to improve prenatal screening are suggested. Furthermore, future research areas, such as correlation with placenta pathology, are presented.