The placenta in fetal congenital heart disease

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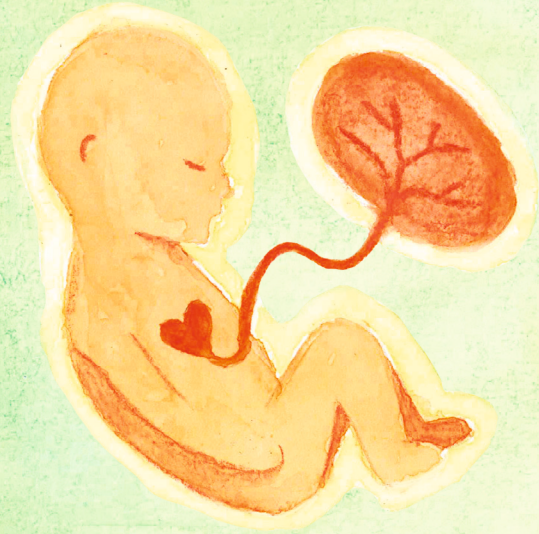

CHAPTER 11

Summary
Samenvatting

SUMMARY

Improvements in prenatal diagnostic methods and neonatal care have markedly increased the survival rates of newborns with a CHD. As a result, the emphasis of medical advancements has transitioned to the enhancement of long-term neurodevelopmental outcomes. Neurodevelopmental delay, which is frequently reported in CHD and already present in utero. As placental insufficiency and related pregnancy complications occur more frequently in pregnancies with fetal CHD, it is hypothesized that abnormal placental development contributes to the delayed neurodevelopment that is reported in these cases. By understanding how heart and placenta development interact, we may gain a better comprehension of why congenital heart defects occur. Enhancing our understanding of the etiology of CHD may lead to new strategies to prevent and treat them in an early stage. In **Chapter 1** of this thesis, this topic is illustrated in the general introduction of this thesis.

A systematic review and overview of the literature on fetal CHD and placenta development are presented in **Chapter 2**. Fetal CHD is related to microscopic placental abnormalities and altered expression of angiogenic biomarkers in maternal serum and umbilical cord blood. Furthermore, altered gene expression involved in placental development, fetal organ development and fetal growth are found in maternal serum and placental tissue of fetal CHD cases. As the complex developmental pathway of CHD, placentation and neurodevelopment remains largely hypothetical, this highlights the necessity of further studies on this relation.

In **Chapter 3**, a pilot study is presented in which histological placental characteristics of CHD cases are evaluated and compared to placentas of healthy controls. Significantly more delayed maturation, maternal vascular malperfusion, fetal hypoxia and Doppler abnormalities was present in cases with fetal CHD. This was clinically related to reduced umbilical artery flow and brainsparing. In addition, higher placenta severity scores are observed in CHD cases. To assess the effect of aortic oxygenation and flow, cases are divided into two subgroups based on cardiac diagnoses (one group including mostly cases with simple transposition of the main arteries and one group including cases with mainly hypoplastic left heart syndrome and aortic arch hypoplasia). Strikingly, there are no differences in placental abnormalities, fetal growth and fetal Dopplers between those two hemodynamic groups.

As a sequel to this pilot, a prospective study with a large set of consecutive included CHD cases is presented in **Chapter 4.** This study confirms our results as placental and umbilical cord abnormalities are more common in our fetal CHD cases as compared to controls. Even in less severe types of CHD with little or no alterations in hemodynamics (for example small ventricle septum defects), more placental and umbilical cord abnormalities are found. When allocating the CHD cases into subgroups based on

aortic flow and hemodynamics, subgroups based on embryological development and subgroups based on morphology, no significant relations can be found. These observation suggest that placental and umbilical cord abnormalities in fetal CHD cannot solely be attributed to hemodynamic alterations in the fetal circulation caused by the altered anatomy of the CHD. With these results and the current theories on the placental heart axis, it is postulated that altered placental development in these cases is related to early embryological abnormal developmental pathways of the placenta and the fetal heart. Especially, placenta insufficiency is proposed to be an important contributing factor to delayed neurodevelopment in fetal CHD, higher incidence of fetal growth restriction and pre-eclampsia in these pregnancies.

In **Chapter 5**, mRNA expression of candidate genes related to (chronic) hypoxia and/or angiogenesis in placental tissue of fetal CHD is performed, aiming to further elaborate the hypothesis regarding the shared (genetic) developmental pathways of fetal CHD and the placenta. We successfully optimized and validated this technique in placental tissue, enabling numerous opportunities for research (vascular) placenta development. However, we could not establish a correlation between fetal CHD and the expression of the candidate genes in placental tissue. Future projects focusing on full RNA sequencing and/or DNA methylation analyses are suggested to identify genes and molecular pathways that may be linked to fetal CHD and (abnormal) placental development.

Possibly ascribed to placental factors, placental related pregnancy complications are more common in pregnancies that are affected by fetal CHD. In **Chapter 6** the primary causes of fetal demise in CHD cases from the PRECOR registry is explored. As expected, cardiac failure as a result of the heart defect and genetic abnormalities are the most frequent causes of demise in fetal CHD. Nonetheless, we established placental insufficiency as a third contributing factor. As a response to a Letter to the Editor, in **Chapter 7** we explain that the incidence of fetal demise, fetal growth restriction, pregnancy related hypertension and preeclampsia in the PRECOR registry, our cohort of CHD cases, is higher as compared to reference values of the Dutch and/or European population.

In **Chapter 8** an overview of pregnancy related complications within our CHD cohort is provided. Though pre-eclampsia, pregnancy induced hypertension, fetal growth restriction and fetal demise are more common in our CHD cohort as compared to reference values, no relationship could be established between fetal aortic flow and oxygenation and these conditions. A high incidence of placenta-related complications is observed even in minor CHDs without significant hemodynamic consequences, such as small ventricle septum defects. These results support the theory that similar early embryological developmental pathways of the placenta and the fetal heart might contribute to altered placental development, leading to placenta-related complications in these cases.

In **Chapter 9**, an experimental setup is described using a unique animal model. This model allows for the comparison of histological placental characteristics between intervention lambs with an induced hypoplastic heart and healthy control lambs. In future research, we aim to use this model to determine whether placental abnormalities in CHD occur in early embryogenesis or are, at least partially, due to altered hemodynamics resulting from the heart defect.

Chapter 10 provides a general discussion on placental development and placenta related complications in fetal CHD and (angio)genetic factors that influence these developmental pathways. Finally, clinical implications and future perspectives are presented.