The placenta in fetal congenital heart disease

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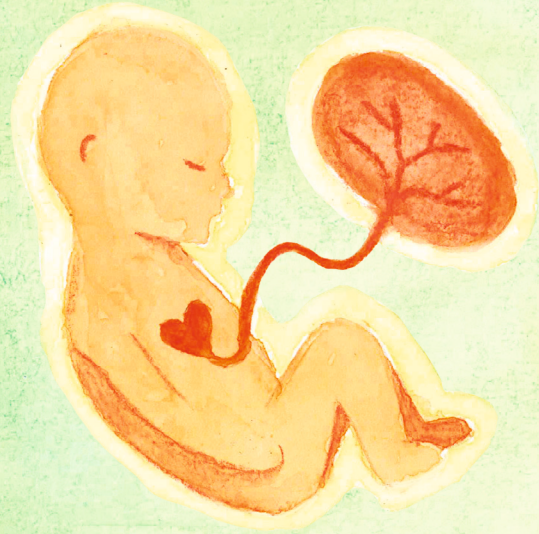

CHAPTER 1

General Introduction

The prevalence of congenital heart defects (CHD) is around 5-8 per 1000 live births, of which approximately a third are severe. Their treatment entails significant risks, making CHD a major contributor to infant mortality globally[1, 2]. Advancements in intensive care unit (ICU) treatment, cardiothoracic surgery, and prenatal detection have significantly improved survival rates for affected newborns. Consequently, the focus of medical innovation has shifted from increasing survival rates to enhancing long-term neurodevelopmental outcomes[1-3].

Neurodevelopmental outcomes in CHD

A critical aspect of morbidity and long-term outcomes in children and adolescents with CHD is neurodevelopmental delay, which is reported in a 40% of cases[4-9]. This concern has become an integral component of prenatal counseling for expectant parents, providing them with crucial information on potential future challenges[10]. In earlier literature this impairment was attributed to the adverse effects of complex cardiothoracic surgeries performed early in life[4, 5, 7]. However, more recent findings indicate that CHD fetuses and newborns exhibit decreased prenatal and postnatal head circumference and delayed cortical maturation on prenatal ultrasound and MRI before undergoing surgery[5-9]. The hemodynamic effects of altered anatomy in CHD causes intrauterine exposure to reduced blood flow and/or low oxygen saturation. Such exposure may be a significant contributing factor to the observed neurodevelopmental delays.

Placenta development in fetal CHD

Next to fetal neurodevelopmental delay, pregnancies with fetal CHD show an increased incidence of fetal growth restriction (FGR), pre-eclampsia (PE), and pregnancy-induced hypertension (PIH)[11-13]. These indicators of impaired placental development are corroborated by findings of increased umbilical artery resistance and reduced global placental perfusion in fetuses with CHD[14-20]. The heightened incidence of placental pathology in these pregnancies warrants further investigation into whether it contributes to impaired neurodevelopment, as increased placental resistance in CHD fetuses is linked to altered neurodevelopmental outcomes[21, 22].

The etiology of CHD is complex and multifactorial, involving both environmental factors and genetic predispositions[23]. The relationship between placental characteristics, placental function, and fetal neurodevelopment in CHD cases remains underexplored and largely hypothetical. Placental abnormalities are thought to be the result of abnormal flow in CHD cases, though on the other hand, early placental factors can contribute to altered heart development. Common developmental pathways of the placenta and the fetal heart are described. It is hypothesized that altered circulation due to the changed anatomy of the heart defect could lead to reduced placenta perfusion, resulting in abnormal placenta development[24, 25]. In that case, abnormal placentation in CHD cases may be due to angiogenic imbalance and altered vascular formation in the placenta, as a result of epigenetic influences due to vascular and circulatory alterations or

hypoxic stress during early embryogenesis [26-28]. Hemodynamic effects of CHD may cause epigenetic changes, leading to altered vascular developmental pathways, angiogenic alterations, placental abnormalities and ultimately, neurodevelopmental delay. The second hypothesis is based on processes in early embryogenesis that influence both the development of the heart and the placenta. Factors contributing to cardiogenesis may also impact placental development and influence the epigenetics of placental tissue, as common genetic factors have previously been identified [27, 29, 30].

Through investigation of the simultaneous progression of congenital heart defects and abnormalities in placental development, a deeper understanding of the etiology of congenital heart defects can be gleaned. This research holds promise for elucidating the underlying mechanisms that give rise to congenital heart defects. By unraveling the interplay between cardiac and placental development, the fundamental question of why congenital heart defects manifest can be further addressed. Such research endeavors are of crucial importance in advancing our knowledge of congenital heart diseases and may pave the way for the development of novel preventive and therapeutic strategies aimed to reduce their occurrence and impact.

Aortic flow and oxygenation and placenta development in fetal CHD

It is hypothesized that diminished cerebral blood flow or decreased oxygenation in the ascending aorta during fetal life contributes to the neurodevelopmental delay. Recent studies on fetal brain development in CHD have shown that FGR and placental insufficiency have a more significant impact on fetal brain growth than aortic flow and oxygenation [5, 6, 8, 31]. Therefore, in this thesis it is investigated whether fetal growth restriction and abnormal placental development are present across all types and severity of CHD. Altered placentation in CHD, rather than solely altered aortic flow and oxygenation, may influence brain growth and development.

By comparing placenta and umbilical cord characteristics in different types of CHD, the effect of aortic hemodynamics on placental development can be assessed or ruled out. Furthermore, it is important to take placenta-related complications such as pre-eclampsia, pregnancy-induced hypertension and stillbirth into account. By assessing these complications in all types of CHD, and not restrict this research to the severe CHD and/or CHD with hemodynamic alterations, more cohesive clinical recommendations can be formulated for monitoring placental function and fetal biometry in cases with fetal CHD. This inclusive approach holds promise to establish more robust clinical protocols aimed at optimizing perinatal outcomes in this vulnerable patient population.

OUTLINE

The aim of this thesis is to understand the relation between the interaction of CHD and placental development and neurodevelopment, by assessing placental characteristics and placenta related complications in pregnancies with fetal CHD.

In **Chapter 2**, the results of a systematic review and overview of the literature on isolated CHD and placenta development is presented, including macroscopic and microscopic placenta characteristics, angiogenic biomarkers and genetic expression in placental tissue.

In **Chapter 3**, a pilot study is presented in which histopathological examination of the placenta of CHD cases is assessed and compared to placentas of healthy controls. To evaluate the hemodynamic effect of the heart defect on the fetal brain in interaction with the placenta, CHD cases are classified into two groups based on aortic flow and oxygenation. As a sequel to this pilot, in **Chapter 4** a prospective study with a large set of consecutive included CHD cases is presented. In this study macroscopic and histological features of the placenta and umbilical cord are studied and related to aortic flow and oxygenation, embryology and etiology of the different types of CHD.

mRNA expression assessment is explored as a novel technique to assess molecular changes related to hypoxia and angiogenesis in placental tissue of pregnancies with fetal CHD in **Chapter 5** of this thesis.

To assess the contribution of placental insufficiency on stillbirth in CHD, stillbirth cases with fetal CHD are identified from a large multicenter fetal and neonatal CHD cohort (PRECOR) in **Chapter 6** and for all cases, it is evaluated whether placental factors might have contributed to the fetal demise. As a response to a Letter to the Editor, the incidence of isolated congenital heart disease and placental insufficiency within the cohort is assessed and related to cases of CHD with stillbirth in **Chapter 7**. To further evaluate placental related complications in pregnancies with fetal CHD, in **Chapter 8** an overview of these complications within our CHD cohort is provided and the complications are related to the types of CHD, based on aortic flow and oxygenation.

In **Chapter 9**, an experimental set up is described with a unique animal model, in which histological placental characteristics of intervention lambs with an induced hypoplastic heart can be compared to that of healthy control lambs, in order to differentiate whether placental abnormalities in CHD occur solely in early pregnancy, or (partially) as a result of altered hemodynamics due to the heart defect.

Finally, in **Chapter 10** a general discussion is provided.

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