The placenta in fetal congenital heart disease

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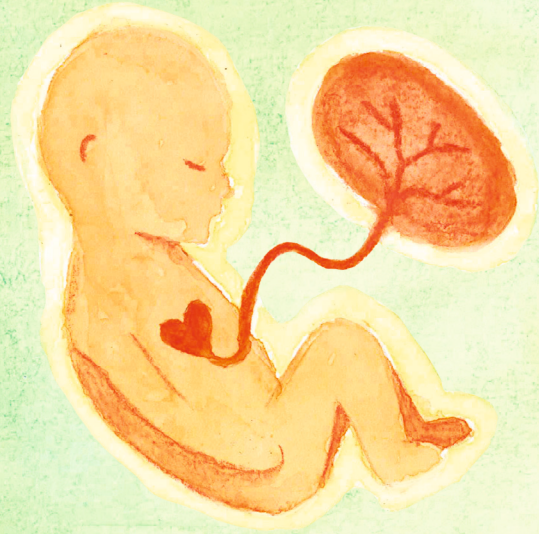

CHAPTER 10

General Discussion

Congenital heart defects (CHD) are the most frequently occurring congenital anomalies, affecting five to eight per thousand live births. 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 from merely improving survival rates to also focusing on the enhancement of long-term neurodevelopmental outcomes. A significant factor influencing morbidity and long-term outcomes in children and adolescents with CHD is neurodevelopmental delay, which is observed in a large amount of cases [1, 2]. This issue has become a key element of prenatal counseling for expectant parents, offering essential information about potential future challenges. Moreover, focus has shifted to the key question of why and among whom congenital heart defects manifest, in order to establish a foundation for the development of novel preventive and therapeutic strategies aimed to reduce their occurrence and impact.

Placental development in fetal congenital heart disease

In addition to fetal neurodevelopmental delay, fetuses with a CHD exhibit a higher incidence of fetal growth restriction (FGR), pre-eclampsia (PE), and pregnancy-induced hypertension (PIH) [3-5]. These indicators of compromised placental development and function are supported by evidence of increased umbilical artery resistance and decreased global placental perfusion in CHD fetuses [6-8]. In general, placental insufficiency is related to delayed fetal neurodevelopment [9, 10]. In pregnancies with fetal CHD, the higher prevalence of placental pathology suggests a potential role for placental factors on the found impaired neurodevelopment in these cases.

Previous studies have documented a higher frequency of placental abnormalities in cases with fetal CHD as compared to normal pregnancies. Chapter 2 provides an overview of a systematic review of the literature on placenta characteristics in pregnancies with fetal CHD. Yet, previous studies often suffered from small sample sizes, lacked representation of all CHD types, and did not differentiate between diagnostic subgroups. Additionally, they frequently did not include a control group for comparison and failed to investigate all macro- and microscopic aspects of the placenta. Therefore, in 2020 a biobank was set up in our center, in which all prenatally detected CHD cases that were born in the LUMC were included consecutively. In this biobank, clinical data and placental tissue of all pregnancies with fetal CHD are collected and stored. Moreover a group of healthy controls were included. In collaboration with colleagues from the University Medical Center Utrecht, we combined our data and conducted a pilot study to evaluate the hemodynamic impact of two different types of heart defects on the fetal brain in interaction with the placenta (Chapter 3). CHD cases were categorized into two distinct groups: (1) CHD resulting in reduced oxygenation in the ascending aorta with normal cerebral blood flow, including simple transposition of the great arteries; and (2) CHD leading to decreased cerebral blood flow with either mixed or normal oxygenation in the ascending aorta, including hypoplastic left heart syndrome, aortic valve stenosis and

aortic arch hypoplasia. We validated observations described in prior literature and found a higher prevalence of abnormal umbilical cord insertion, delayed villous maturation, maternal vascular malperfusion lesions (MVM), and signs of fetal hypoxia in placentas from pregnancies affected by fetal CHD. These observations support the hypothesis that vascular development is altered in placentas of pregnancies with fetal CHD. However, our study did not identify significant abnormalities in placental abnormalities, among the CHD subtypes. In addition, abnormalities in fetal growth parameters and Doppler examination of the umbilical artery and middle cerebral artery were more frequently observed in CHD cases as compared to healthy controls, but did not differ between the two groups of CHD either. The results of this pilot study imply that placental abnormalities identified in pregnancies with fetal CHD may not be attributable to hemodynamic changes occurring in the fetal circulation as a consequence of the CHD. These findings encouraged further research into the effect of fetal hemodynamic changes on placental characteristics in fetal CHD.

As a sequel to this pilot, we performed a prospective study, comprising all cases included in the LUMC (CAHAL) biobank (Chapter 4). In this study, a large cohort of consecutively included fetuses and a large control group was included. In addition to histological placental characteristics, vascular patterning of chorionic blood vessels and umbilical cord coiling were analyzed. In consistence with findings from previous research, our study revealed a greater prevalence of placental abnormalities in CHD cases compared to healthy controls. Those abnormalities included lower placenta weight, abnormal (velamentous and marginal) umbilical cord insertion, single umbilical artery (SUA), delayed villous maturation, maternal vascular malperfusion (MVM), fetal vascular malperfusion (FVM), inflammatory lesions and higher placenta severity scores (developed by Nijman and van der Meeren et al. [11] to indicate the extend and severity of placental abnormalities per individual case). Again, the found abnormalities could not be correlated with specific cardiac diagnoses determined by aortic flow and oxygenation. We analyzed the placenta morphology according to different CHD subgroups based on embryological development and morphology, but again all subgroups were comparable irrespective of different group allocations. This suggests that placental abnormalities identified in CHD cases cannot be attributed to hemodynamic or developmental subgroups. We observed variations in the incidence of FVM, characterized by thrombosis in the fetal vascular placental circulation, across all hemodynamic CHD groups. FVM is associated with fetal cardiac insufficiency and in cyanotic CHD changes in placental blood flow and oxygenation are observed [12]. In fetuses with CHDs affecting the aortic flow and oxygenation, there can be an altered fetal circulation, resulting from cardiac insufficiency. FVM was described in groups with normal, obstructed/reversed, and mixed aortic flow, as well as in those with normal and mixed aortic oxygenation. Moreover, this anomaly was also observed in the CHD subgroup characterized by normal flow and oxygenation, including cardiac diagnoses that are not related to cardiac insufficiency. Hence, while FVM is influenced by fetal circulation dynamics, our findings suggest that

this placental abnormality cannot be solely attributed to aortic flow and oxygenation in these patients. Next to cyanosis in specific types of CHD, we postulate that altered earlier placental development in CHD may affect fetal circulation and umbilical cord flow, leading to fetal vascular malperfusion. In addition, a remarkable observation was the significantly higher prevalence of magistral chorionic vascular patterns in cases of CHD compared to healthy controls and a significantly greater prevalence of hypercoiling that was observed in CHD cases as compared to controls. Once more, those findings could not be related to specific cardiac diagnoses based on aortic flow and oxygenation. The umbilical cord and coiling begins to form as early as the third week of gestation [13]. Prior studies have associated hypercoiling with restricted umbilical cord flow, FGR, adverse pregnancy outcomes and fetal anomalies, including CHD. Consequently, within our cohort, cases exhibiting hypercoiling demonstrated higher placental severity scores, indicating more placental abnormalities and, ultimately, reduced placenta function. During early embryogenesis, the processes of vascular patterning, coiling, and primary heart tube development occur concurrently [14]. It is conceivable that early hemodynamic alterations in the embryo resulting from developing cardiac defects may induce changes in flow dynamics throughout the embryo and the developing placenta. Conversely, in our cohort chorionic vascular patterning and umbilical cord coiling could not be related to cardiac diagnoses based on aortic flow and oxygenation. Therefore, we postulate that concurrent developmental pathways may influence both placental and embryological/fetal vascular development, rather than being attributed to early hemodynamic alterations due to cardiac anatomy. Moreover, the presence of hypercoiling may lead to reduced umbilical cord flow, potentially affecting placental and fetal circulation and thereby contributing to altered vascular development in both the placenta and the fetus.

In summary, though the hemodynamic effects of a developing CHD in early embryogenesis cannot be completely ruled out, our results suggests that abnormal placental development CHD cases may be a result of earlier embryonic events, before hemodynamics alterations are definitive, influencing both the fetal heart and the placenta, rather than a result of hemodynamic changes occurring in the fetal (aortic) circulation as a consequence of the CHD.

Neurodevelopment in fetal congenital heart disease

It has been suggested that both reduced flow towards the fetal brain and diminished oxygenation in the ascending aorta may contribute to neurodevelopmental delays observed in fetuses with CHD, presumably through a shared mechanism involving hypoxia in the fetal brain. However, alternative research indicates that decreased fetal growth and placental insufficiency exert a more substantial influence on brain growth in fetuses with CHD compared to alterations in aortic flow and oxygenation [15, 16]. Our findings align with this perspective, as the studies demonstrated in Chapter 3 and Chapter 4 no disparities in placental abnormalities, fetal growth, nor fetal Doppler measurements between CHD associated with diminished flow towards the fetal brain

and those resulting in reduced oxygenation in the ascending aorta are observed. Thus, it supports the theory that altered placental function in fetal CHD contributes to the neurodevelopmental delays observed in affected fetuses and infants, possibly alongside fetal hemodynamic alterations caused by the CHD. Nonetheless, given that our studies did not include assessments of fetal brain volumes, further research is warranted to disentangle the respective contributions of altered placental function and fetal cardiac anatomy to impaired brain growth in CHD.

(Angio)genetic factors influencing placental and cardiac development

Numerous genes have previously been identified to influence the concurrent development of both the placenta and the fetal heart. In Chapter 2 of this thesis, an overview is provided of angiogenic biomarkers in pregnancies with fetal CHD and genetic expression in the placenta. Altered expression of angiogenetic biomarkers was found in maternal serum and umbilical cord blood and altered expression of (m) RNA and gene alterations in genes associated with cardiac function, fetal growth, placental and trophoblast development were described. Similar features are evident in pregnancies and placentas associated with FGR, PE and PIH, all finding their origin in abnormal trophoblast invasion and MVM. This implies a correlation between CHD and impaired (early) placentation, potentially resulting in reduced fetal-maternal exchange of oxygen and nutrients. Interestingly, even in the absence of PE and FGR, manifestations of altered placentation and placental insufficiency are described in cases with fetal CHD. The altered RNA expression of genes that are related to the etiology of CHD may underlie pathological changes in the placenta as well, partially mirroring the phenotype of classical placental dysfunction due to inadequate trophoblast invasion. In previous studies examined in the systematic review outlined in Chapter 2, it is described that altered molecular expression in vascular developmental pathways affects vascular development in both the placenta and fetal organs. Changes in protein expression of genes exerting a localized effect on cardiac or placental tissue, as well as alterations in proteins with a broader impact, have been described in placental tissue and maternal serum. These findings suggest an influence on vascular developmental pathways in other fetal organs, alongside the impact on the development of the fetal heart and the placenta. Moreover, impaired placental function and altered vascular expression within the placenta can lead to reduced fetal organ perfusion and hypoxia. Specifically hypoxia and diminished organ perfusion may play a significant role in the delayed development of the brain, given its heightened sensitivity to hypoxic conditions[17, 18]. Additionally, alterations in angiogenesis regulation have been detected in the cerebral tissue of fetal CHD cases in previous literature[19]. An altered angiogenic environment could exacerbate hypoxic stress and hinder microvascular development in the brain, thereby contributing to the delayed neurodevelopment and brain maturation observed in CHD fetuses.

The multifactorial origin of CHD includes contributions from both environmental factors and genetic predispositions. In accordance with the placenta-heart axis theory[20],

alterations in early placentation and fetal hypoxia during the first trimester are contributing factors in the pathogenesis and etiology of fetal CHD and impaired placental development and function [21]. It is feasible that angiogenic imbalance and altered vascular formation in the placenta of CHD cases may stem from epigenetic influences resulting from vascular and circulatory alterations or hypoxic stress caused by the forming cardiac defect during early embryogenesis of CHD cases. The hemodynamic effects of CHD may induce epigenetic modifications, leading to altered vascular developmental pathways, angiogenic alterations and placental abnormalities. Though, once more this causality could also be reversed. Factors implicated in the pathogenesis of CHD appear to influence placental development and impact the epigenetics of placental tissue, as shared genetic contributors have been identified.

To further elaborate on the theory of the placenta-heart axis in relation with genetic expression in placental tissue, we assessed molecular changes related to altered placental development in fetal CHD in Chapter 5. We included placentas from the previously described biobank. By exploring mRNA expression of candidate genes related to (chronic) hypoxia and/or angiogenesis in placental tissue of fetal CHD and relate these to the cardiac diagnoses based on aortic flow and oxygenation, we aimed to assess the effect of aortic hemodynamics on this expression. Though we successfully performed this technique, enabling numerous opportunities for research on (vascular) placenta development, we could not establish a correlation between fetal CHD and these expressions. An explanation for this could be that placental abnormalities in CHD cases are caused by hemodynamic effects of the heart defect and compensatory mechanisms, rather than (angio)genetic changes. Though, as previously stated, shared (epi)genetic pathways influencing both the fetal heart and placental development have been described in previous literature, making this explanation less plausible. Another explanation could be that, aligning with the theory of the placenta-heart axis, circulatory alterations and hypoxia triggered by CHD may influence placental development, resulting in histological changes in placental tissue, particularly in the decidua, that correspond with placental insufficiency. While these alterations may have influenced gene expression and protein pathways, their effect on RNA expression might be relatively insignificant. Another plausible explanation for our findings is that genes other than those assessed in this study could be relevant. Nonetheless, to our knowledge, we examined relevant genes in the association with hypoxia and altered angiogenesis. Subsequent research into genetic expression patterns within placental tissue among CHD cases are crucial for elucidating the association between placental development and the etiology of CHD. This research should involve full RNA sequencing and/or DNA methylation analyses, as these are more intricate methodologies that hold the potential to identify genes and molecular pathways that may be linked to fetal CHD and placental development. In addition, these results should be related to neurodevelopmental outcomes, in order to identify the true factors that influence neurodevelopment in these cases.

Pregnancy related complications in fetal congenital heart disease

Pregnancies with fetal CHD have an increased risk of FGR, PE and PIH, most likely as a result of altered placental development and an increased incidence of placental insufficiency. In addition, CHD is related to abnormal Doppler indices, including increased umbilical artery resistance, and reduced placental perfusion. Unfortunately, fetal demise is significantly more common in cases with CHD as compared to the healthy population. This demise is frequently attributed to cardiac failure in a daily clinical approach, as conditions like atrioventricular septal defects (AVSD) and Ebstein's anomaly are known to cause fetal hydrops and demise. Nevertheless, even smaller defects like ventricular septal defects (VSD) are associated with a higher incidence of fetal demise. In Chapter 6, the primary causes of fetal demise in CHD cases were explored, hypothesizing that cardiac failure or genetic abnormalities may play a significant role, alongside placental insufficiency as a third contributing factor. Cases with CHD and fetal demise were identified in the PRECOR registry, in which all fetal and neonatal cases with CHD from the Center for Heart Abnormalities Amsterdam-Leiden (CAHAL) are included from January 2002. The incidence of fetal demise in our CHD population, excluding aneuploidy (trisomy 13, trisomy 18, triploidy, Turner syndrome), was 1.4%, which is three times higher than the incidence of fetal demise in the overall Dutch population. In these CHD cases, cardiac failure or an underlying genetic syndrome were the primary causes of demise. However, we identified a significant additional factor, namely placental insufficiency, as 10.1% of the CHD cases with fetal demise in our cohort exhibited signs of placental pathology and an absence of cardiac failure. In Chapter 7 the incidence of isolated congenital heart disease and placental insufficiency is assessed and related to cases of CHD with stillbirth, as suggested in a Letter to the Editor. To further elaborate on placenta related pregnancy complications in different types of fetal CHD, we assessed the prevalence of pregnancy complications in pregnancies with fetal CHD and related this to aortic flow and oxygenation in Chapter 8. For this study, cases with a prenatally identified CHD, born between January 2009 and 2023 were extracted from the PRECOR registry and categorized into groups based on aortic flow and oxygenation. In accordance with previous literature, the incidence of FGR, PE, PIH and stillbirth were higher in our cohort as compared to the overall Dutch and/or European population. Remarkably, there was no correlation between those pregnancy complications and cardiac diagnoses based on cardiac hemodynamics. Given that the high incidence of placenta-related complications in pregnancies with fetal CHD cannot be linked to fetal hemodynamics based on aortic flow and brain oxygenation, this study supports the hypothesis that cardiac and aortic hemodynamics have a limited effect on placental development and function in fetal CHD. This finding aligns with the previously described theory that placental development and embryonic heart development occur concurrently and mutually influence each other during early gestation. Altered placental development in fetal CHD may be associated with shared early embryological developmental pathways of the placenta and fetal heart, rather than being solely attributed to hemodynamic changes in the fetal circulation caused by CHD. Consequently, abnormalities in early placental development

could contribute to the prevalence of FGR, PE, PIH and stillbirth in pregnancies with fetal CHD, rather than these conditions being secondary to fetal hemodynamic alterations.

Clinical implications

As stated in this thesis, altered placental development, placental insufficiency and placenta related pregnancy complications such as FGR, PE, PIH and fetal demise are more common in pregnancies with fetal CHD. However, clinicians often focus on these complications primarily in cases of severe CHD, like univentricular heart defects. Our findings indicate that placental insufficiency and associated complications are present across all types of CHD, including those that are hemodynamically less significant. Consequently, it is crucial to thoroughly monitor both maternal and fetal conditions in all pregnancies where fetal CHD is suspected. We recommend regular assessment of fetal growth and Doppler flow measurements, particularly of the umbilical artery and middle cerebral artery, to evaluate placental function in all types of fetal CHD. Additionally, ongoing monitoring of maternal blood pressure and attentiveness for PE-related symptoms should be maintained in these pregnancies.

In fetal CHD, the timing of delivery is crucial to optimize neonatal outcomes. Currently there is a focus on avoiding prematurity, aiming to attain an optimal state of pulmonary maturation and cardiac functionality at delivery. Such favorable conditions are important for the neonate to endure the necessary medical interventions. It is known that term neonates have better outcomes after surgery as compared to preterm neonates [22, 23]. However, in clinical recommendations on timing of delivery in fetal CHD, placental factors have not been taken into account. As illustrated in this thesis, pregnancies with fetal CHD have a higher risk on placental insufficiency and related pregnancy complications. It is known that placental insufficiency can worsen as the pregnancy progresses beyond 40 weeks GA. Post-term pregnancies can exacerbate placental insufficiency, leading to a higher risk of fetal distress, hypoxia, or even stillbirth [24]. Thereby, neonates with CHD often require immediate medical or surgical interventions after birth. Induction of the delivering at term, ensures that the neonate is born in a controlled environment with the necessary medical team and facilities ready to provide the immediate care when needed. In addition, the risks associated with prolonged pregnancy, such as meconium aspiration, can complicate the condition of a newborn with CHD [25]. These additional complications can increase the complexity of managing the neonates heart condition immediately after birth. On the other hand, induction before 37 weeks GA for logistic reasons is unfortunate, as preterm birth is another risk factor for adverse outcomes in neonatal CHD. The decision to initiate labor induction in pregnancies complicated by CHD must consider multiple factors, including maximizing fetal maturity and optimizing conditions for immediate postnatal care. In addition, the risks associated with placental insufficiency at post-term should be taken into account. This complex decision-making process necessitates collaboration among a diverse team of specialists, including obstetricians, neonatologists, and pediatric cardiologists, who can tailor the timing of

delivery to address the specific and individual needs and conditions of both the mother and the fetus. As these complications are rare, it is unfeasible to perform a decent RCT on this topic. Nonetheless, we strongly advocate for clinicians to consider labor induction at the term in pregnancies with a fetal CHD to reduce the potential complications stemming from placental insufficiency in post-term pregnancies. Again, this recommendation holds relevance across all forms of CHD and should not be limited to severe CHD cases.

In addition, and as stated in Chapter 6, clinicians should pay attention fetal demise in cases with fetal CHD. Considering that demise in cases with fetal CHD is not necessarily attributable to the heart defect itself, it is important to systematically assess the cause of the demise rather than hastily attributing it to the heart defect. Placental insufficiency can significantly contribute to fetal demise, making histological examination of the placenta essential for identifying the precise cause of fetal demise. Physicians should stress the importance of placental pathology examinations and advocate for parental consent to these noninvasive procedures, particularly in cases where the cause of death is not so clear. Furthermore, it is crucial to differentiate between MVM and FVM during placental pathology examinations to enhance the understanding of placental function and the underlying cause of demise. Detailed information on placental function in pregnancies ending in fetal demise is thereby vital for informing the clinical management and monitoring of future pregnancies, as it may have significant implications for both the mother and subsequent fetuses. Additionally, large national registries are important to enable systematic approach to these relatively rare events.

Another significant clinical consequence of abnormal placentation during fetal development is the increased susceptibility to cardiovascular disease and insulin resistance in later childhood and adulthood. Abnormal placentation is associated with poor fetal growth and low birth weight and according to Barker's hypothesis, such conditions in fetal life are linked to the development of diabetes, obesity, hypertension, and coronary artery disease in adulthood [26, 27]. Given that CHD is often correlated with abnormal placentation, it stands to reason that patients diagnosed with CHD may face an increased risk of developing the aforementioned conditions in addition to their congenital heart defect later in life. This dual vulnerability underscores the necessity for a nuanced approach to the long-term health management of individuals with CHD. To accurately identify patients at heightened risk for cardiovascular disease and to prioritize preventive measures effectively, it is important to conduct in-depth studies into the long-term cardiovascular outcomes of individuals with CHD. Such research is crucial, not only for understanding the extended health implications of CHD but also for formulating targeted interventions that can anticipate on these risks. These interventions might include regular monitoring of cardiovascular health, early lifestyle modifications, and possibly pharmacological strategies tailored to the specific needs of individuals with CHD. By advancing our understanding of the long-term impacts of CHD, healthcare providers can better manage and improve the quality of life for these

patients, ultimately reducing the incidence and severity of cardiovascular complications associated with both CHD and abnormal placentation.

Future perspectives

As elucidated in this thesis, CHD correlates with disruptions in (angio)genetic and vascular placental development. Consequently, pregnancies affected by CHD have a higher incidence of placental insufficiency and pregnancy complications directly associated with the placenta. Altered placental development and reduced placental function may, partly, contribute to the delayed neurodevelopment found in these cases that is already present in utero.

Future research aimed at improving the (neuro)developmental outcomes in fetal CHD, should integrate assessments of placental morphology, fetal biometry, and placenta-related complications such PE and relate this to the (neuro)developmental outcomes. Furthermore, the inclusion of functional imaging data is essential for a better comprehension of in vivo alterations in flow and oxygenation as a result of the CHD, across critical areas like the aortic arch, the fetal brain and the placenta. This information is essential to assess the contributions of altered placental function and altered fetal cardiac anatomy and circulation to delayed neurodevelopment in CHD. Thereby, the animal model described in Chapter 9 of this thesis is an optimal model to identify the pure effect of the hemodynamic changes caused by the CHD, as in this fetal lamb model hypoplastic left heart syndrome (HLHS) is induced in utero[28]. This animal model provides a unique opportunity to examine and compare the placentas of HLHS lambs with those of healthy counterparts, under identical conditions (twins in same mother sheep). Animal models like these are essential in research on the pure impact of the cardiac defect on flow patterns and organ development in CHD and are therefore crucial in future research on this topic.

In addition, future research on placental development in CHD should take angiogenesis and genetical predispositions of the placenta and the fetal organs into account. The heart and the placenta develop concurrently during embryogenesis and angiogenesis is crucial for the growth and development of both organs. Genetic factors play a significant role in orchestrating this intricate process. As many signaling pathways and molecular mechanisms are involved in angiogenesis and vascular development are shared between the placenta and the developing heart, disruptions in these pathways can affect both organs simultaneously, leading to CHD and placental abnormalities. Alternatively, abnormalities in placental vascular development can compromise fetal cardiac function, contributing to the development of CHD. A better understanding of these (angio)genetic developmental pathways and relationships is vital for gaining insight into the mechanisms underlying the development of CHD and understanding its origins. This information is crucial for developing strategies to prevent and/or reduce the impact of CHD in utero, during the crucial neonatal period and throughout the entire lifespan of individuals with CHD.

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