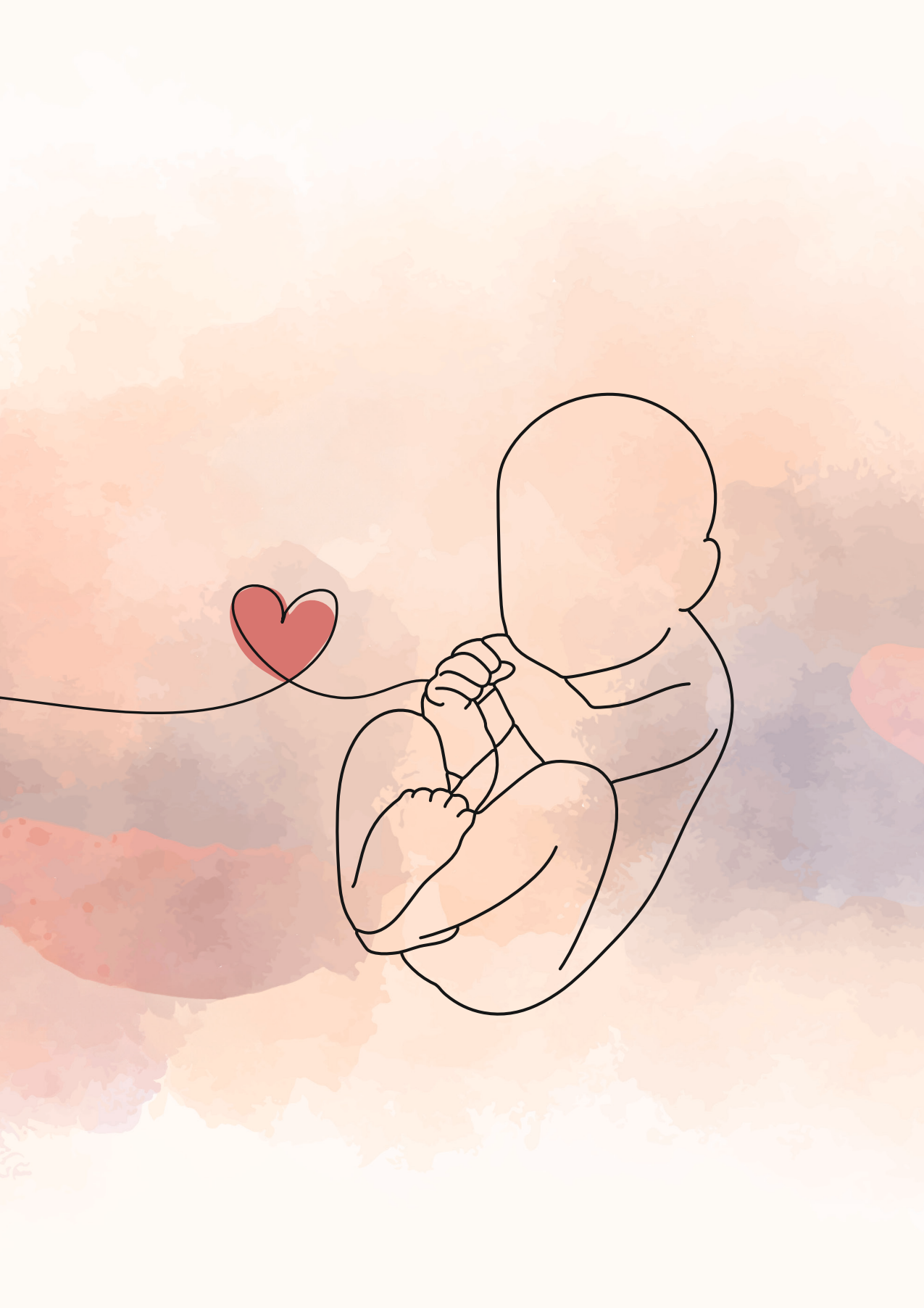
Congenital heart defects: from a prenatal perspective

Nisselrooij, A.E.L. van



APPENDICES

SUMMARY

This thesis discusses the prenatal detection and outcome of congenital heart defects in the fetus.

This thesis is divided into two parts. *The first part focuses on determinants for a prenatal diagnosis in fetus with a structural congenital heart defect, whereas the second part elaborates on the prognosis of congenital heart defects in the fetus to improve prenatal counseling and postnatal care management.*

Prenatal detection

In **chapter 2** we present a case-control study that assessed the quality of fetal heart images and circumstantial factors in fetuses with prenatally undetected and detected congenital heart defects. Cardiac images were scored for technical correctness by two fetal echocardiography experts, blinded to prenatal detection and the specific cardiac diagnosis. Our results show that circumstantial factors, such as BMI or fetal position, hardly differed between prenatally undetected and detected cases. The group of undetected cases however, scored significantly lower than the detected group on the quality of all cardiac images obtained. A lack of adaptational skills when performing the cardiac scan appeared the main cause for a missed prenatal diagnosis (49%), followed by the inability to recognize the heart defect (31% of undetected cases). Prenatal detection appeared not feasible in 20% of undetected cases, as the heart defect was not visible at mid-gestation on adequate cardiac scans. Furthermore, the performance of a high volume of cardiac scans, especially in large ultrasound centers, significantly contributes to prenatal detection.

Outcome

This second part aims to provide evidence on the prognosis of fetal congenital heart defects, as prenatal counselling can be particularly challenging for diagnoses with limited evidence on outcome from a prenatal perspective.

In **chapter 3** we report on the prevalence of genetic diagnoses in fetus with severe congenital heart defects, either isolated or non-isolated, as well as the impact of these diagnoses on mortality and morbidity. After exclusion of aneuploidy cases, a genetic diagnosis was found in 16% of cases, comprising copy number variants in 10% and abnormalities in specific genes in 6% of cases. Therefore, exome sequencing should be considered in all fetuses with a normal chromosome microarray analysis, especially if extra-cardiac malformations are present.

In **chapter 4** we present our response to a Letter to the editor. With the use of the acquired data from chapter 3, we provide additional information on genetic syndromes, particularly those not detectable with chromosome micro-array analyses. The incidence of CNVs and sequence variants is reported for each CHD diagnosis, and sequentially for isolated and non-isolated cases separately. With regards to specific CHD diagnoses, exome sequencing had a particularly high yield amongst those with conotruncal anomalies, left isomerism and rhabdomyomas.

Chapter 5 involves a retrospective cohort study that assessed the impact of extracardiac pathology on fetal head growth and growth in general, as a marker for fetal brain development. Patients were allocated to the isolated group or assigned to one of the three non-isolated groups (genetic syndromes, extra-cardiac malformations or placental pathology). A mixed-linear regression model was used to study fetal growth over time. At mid-gestation, head circumference was significantly smaller in non-isolated compared to isolated cases, which decreased significantly further with advancing gestation. Placental pathology and genetic syndromes seem to be important attributors for restricted (head) growth. This effect appears irrespective of altered hemodynamics caused by the CHD.

In **chapter 6** we describe a case-control study to evaluate postnatal outcome of fetus with an isolated ventricular size disproportion, particularly those that do not develop an aortic coarctation. In this cohort, 60% of fetus did not develop an aortic coarctation. These cases showed prenatally undetected congenital defects and pulmonary or transition problems. Proper monitoring is therefore warranted and prenatal counseling should consider to incorporate the risks for additional morbidity and neonatal complications in these cases.

Chapter 7 reports our original cohort study to assess the mortality and postnatal morbidity in fetus with a common arterial trunk. Additionally, we performed a systematic review of the literature for additional cases. This study found that parents opted for elective pregnancy termination in almost half of the cases. Amongst ongoing pregnancies, 40% resulted in fetal or neonatal demise. Significant morbidity, such as 22q11 deletion syndrome, Adams-Oliver syndrome, intestinal atresia and neurodevelopmental delay, was found in 40% of survivors.

In **chapter 8**, we present an international case series of fetuses diagnosed with an aorto-left ventricular tunnel (AVLT) to provide evidence on the outcome of this rare diagnosis, especially before birth. We evaluated antenatal parameters, neonatal outcome, postnatal follow-up in these cases and systematically reviewed the literature

for similar cases. Echocardiographic characteristics of AVLT included an increased cardiac-thorax ratio (95%), increased left ventricular end-diastolic diameter (90%) and a dysplastic aortic valve (90%). Extracardiac malformations were rare (5%). All cases that resulted in fetal demise, showed signs of hydrops prior to 24 weeks of gestation or at autopsy. In the absence of fetal hydrops, however, ALVT generally carries a good prognosis.