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### Seeing the unseen

*The importance of prenatal screening*

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CHAPTER  
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EARLY DETECTION OF ISOLATED  
SEVERE CONGENITAL HEART DEFECTS IS  
ASSOCIATED WITH A  
*lower threshold to terminate the pregnancy*

## Abstract

**Introduction:** Early detection of isolated severe congenital heart defects (CHDs) allows for extra time for chromosomal analysis and informed decision making, resulting in improved perinatal management and patient satisfaction. Therefore, the aim of this study was to assess the value of an additional first-trimester screening scan compared to only a second-trimester scan in fetuses diagnosed with isolated severe CHDs. Prenatal detection rate, time of prenatal diagnosis and pregnancy outcome were evaluated in the Netherlands after implementation of a national screening program.

**Materials and Methods:** We performed a retrospective geographical cohort study and included 264 pre- and postnatally diagnosed isolated severe CHD cases between January 1, 2007 and December 31, 2015, in the Amsterdam region. Severe CHD was defined as potentially life threatening if intervention within the first year of life was required. Two groups were defined: those with a first- and second-trimester anomaly scan (group 1), and those with a second-trimester anomaly scan only (group 2). A first-trimester scan was defined as a scan between 11+0 and 13+6 weeks of gestation.

**Results:** Overall, the prenatal detection rate for isolated severe CHDs was 65%; 63% were detected before 24 weeks of gestation (97% of all prenatally detected CHDs). Prenatal detection rate was 70.2% in the group with a first- and second-trimester scan (group 1) and 58% in the group with a second-trimester scan only (group 2) ( $p < 0.05$ ). Median gestational age at detection was 19+6 (interquartile range (IQR) 15+4 - 20+5) in group 1 versus 20+3 (IQR 20+0 - 21+1) in Group 2 ( $p < 0.001$ ). In group 1, 22% were diagnosed before 18 weeks of gestation. Termination of pregnancy rate in group 1 and group 2 were 48% and 27%, respectively ( $p < 0.01$ ). Median gestational age at termination did not differ between the two groups.

**Conclusion:** Prenatal detection rate of isolated severe CHD and termination of pregnancy rate was higher in the group with both a first- and second-trimester scan. We found no differences between timing of terminations. The additional time after diagnosis allows for additional genetic testing and for optimal counselling of expectant parents regarding the prognosis and perinatal management so that well-informed decisions can be made.

## Introduction

A congenital heart defect (CHD) could severely compromise survival, being the primary cause of infant mortality.<sup>1-4</sup> It is the most common congenital anomaly with a prevalence of 5-8 per 1000 deliveries.<sup>5</sup> Severe CHDs, defined as the need for surgical repair in the first year of life, account for a third of these cases.<sup>6</sup> Presently, many CHDs are diagnosed prior to birth, given the ubiquity of a second-trimester anomaly scan in most high-income countries.<sup>7</sup> A prenatal diagnosis reduces mortality and results in a more favourable long-term outcome compared to when the CHD is diagnosed postnatally.<sup>8-11</sup>

Early prenatal detection of CHDs has been improved by the introduction of structured heart protocols, advanced experience of sonographers and the improved quality of ultrasound machines.<sup>12-15</sup> In the Netherlands, the prenatal detection rate for CHDs increased substantially after implementation of the 20-week scan<sup>16,17</sup>, and with the introduction of the three vessel view as a mandatory screening view in 2012.<sup>18</sup> The principal benefit of early prenatal detection is the time for further delineation of the heart defect, genetic analysis, and planning of perinatal management.<sup>19,20</sup> It enables parents to make informed decisions, and allows if desired, for timely termination of pregnancy (TOP) which is safer for the mother and has fewer psychological consequences.<sup>21,22</sup>

Despite the increasing emphasis on prenatal detection of isolated severe CHDs, a significant number of cases are still missed worldwide.<sup>7,17</sup> The reported prenatal detection derives from cohort studies evaluating the second-trimester anomaly scan<sup>16,23</sup>, due to lack of reimbursement for a first-trimester anomaly scan in national screening programmes.<sup>24</sup> Studies reporting on CHD detection in the first-trimester focus mainly on markers and patients at high risk for cardiac malformations.<sup>25,26</sup>

Although the prenatal detection rate for isolated severe CHDs is well-studied<sup>16,17</sup>, the impact of a first-trimester anomaly scan in addition to a second-trimester anomaly scan, is unclear. We aimed to determine the effect of an additional first-trimester scan on prenatal detection rate, timing of prenatal diagnosis and pregnancy outcome of isolated severe CHDs in the Amsterdam region in the Netherlands.

## Methods

### Design and setting

We performed a retrospective geographical cohort study at the Amsterdam UMC - Location AMC, a Fetal Medicine Unit, and its affiliated centres in the Northwest region of the Netherlands. These centres provide care to approximately 16.000 pregnant women per year. The Amsterdam UMC works closely together with the Leiden University Medical Center (LUMC) to provide optimal care for children with CHD. The collaboration between these three Fetal Medicine Units is called CAHAL (Center for congenital heart defects Amsterdam and Leiden, in Dutch: Centrum voor Aangeboren Hartafwijkingen Amsterdam-Leiden). Details on all pre- or postnatally detected CHDs are gathered in the CAHAL fetal/

neonatal database called PRECOR. The method used for data collection in the CAHAL cohort has been previously reported by van Velzen et al.<sup>17</sup> If data was incomplete, additional information was collected through referral centers or midwifery practices. This manuscript has been written according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.<sup>27</sup> Since 2007, the screening program in the Netherlands has been centrally organized with a uniform protocol and regulations regarding training and quality monitoring. The performance of two ultrasound scans is financially supported by the government: A dating scan around 10 weeks of gestation and a second-trimester anomaly scan for detection of structural anomalies. Prenatal screening for fetal aneuploidies is voluntary and, during this study protocol, solely performed with first-trimester combined testing (FCT), as Non-Invasive Prenatal Testing (NIPT) was used from 2017 onwards. We defined a first-trimester scan as any ultrasound performed by a certified sonographer between 11+0 and 14+0 weeks of gestation, irrespective of the indication, i.e., no distinction was made between women opting for FCT, women with a family history of congenital anomalies or women who voluntarily opted for a first-trimester scan. All first-trimester scans were performed abdominally. In case of poor visibility, the fetus was also examined transvaginally. There was no national guideline for assessment of organ systems (or fetal echocardiography) in the first-trimester<sup>28</sup>, but measurement of crown-rump length (CRL) and nuchal translucency (NT) were performed according to a standardized national protocol and the Fetal Medicine Foundation (FMF) criteria.<sup>29,30</sup> The reimbursed second-trimester anomaly scan was performed between 18 and 22 weeks, preferably around 19 weeks of gestation, according to a standardized protocol.<sup>28</sup> The examination of the fetal heart consisted of visualizing several cross-sectional mandatory planes. The first mandatory plane was the four-chamber view with the size and position of the heart in the thorax, the symmetry of the atria and ventricles, and identification of the atrioventricular valves and crux. Secondly, the left and right cardiac outflow tracts were visualized.<sup>31</sup> In January 2012 the 3VV was added as a mandatory plane, obtained in a transverse plane, cranial to the four-chamber view.<sup>31</sup> CHDs were classified as severe if surgery was required within the first year of life (or likely to be required in the case of pregnancy termination). If CHD was suspected patients were referred to a Fetal Medicine Unit for a level 2 ultrasound, followed by echocardiography and counselling by a pediatric cardiologist after confirmation of the diagnosis. Cases with a NT  $\geq 3.5$  mm (>99th percentile) or an increased risk of fetal aneuploidies were also referred. In all cases chorionic villus sampling or amniocentesis for fetal DNA analysis was offered. Patients underwent in depth counselling about the short - and long term prognosis of their child. All management options were discussed, including pregnancy termination which is allowed until 24 weeks of pregnancy in the Netherlands. Parents with an ongoing pregnancy were advised to deliver in a tertiary center with a neonatal intensive care unit and paediatric cardiology and paediatric cardiac surgery management facilities as indicated. All cases with a NT  $\geq 3.5$  mm and a normal 20-week scan were offered a third trimester scan for additional cardiac evaluation.

### Study Group

We included isolated CHDs in the Amsterdam region between January 1, 2007, and December 31, 2015. We chose this period since a national screening program is running in the Netherlands from 2007 onwards. Fetuses with a chromosomal defect or associated structural anomalies were excluded, as knowledge of their presence could have led to a more thorough cardiac examination and therefore biased the detection rate determination. All women in this study received a structured second-trimester anomaly scan. We defined two groups of isolated severe CHDs: Those with a first- and second-trimester anomaly scan (group 1), and those with a second-trimester anomaly scan only (group 2).

### Data collection and classification of cardiac abnormalities

Baseline characteristics were prospectively added to the registry immediately after prenatal ultrasound diagnosis or treatment at a center for pediatric cardiology for postnatal cases. These characteristics included maternal age, gestational age (GA) at detection, performance of first-trimester screening, GA of CHD detection and prenatal diagnosis. Data on pregnancy and neonatal outcomes, such as GA at birth, presence of dysmorphic features, and, if applicable, post-mortem reports, were collected from medical records. Cardiac abnormalities were classified according to the dominant heart lesion (for example, a coarctation of the aorta combined with a small ventricular septal defect was coded as an aortic coarctation). When autopsy was not performed after TOP, the heart defect was categorized by its prenatal diagnosis. We reviewed all included isolated severe CHD cases with consultation of a pediatric cardiologist, to ensure the correct CHD diagnosis and coding. The postnatal diagnoses were coded and categorized based on the description of van Velzen.<sup>17</sup> Cases with additional congenital anomalies were excluded. Fetuses with soft markers including a single umbilical artery, increased NT, abnormal ductus venosus flow, tricuspid regurgitation, increased heart rate, absence of the nasal bone, echogenic small bowel and pyelectasia were included in the analysis. Similarly, accompanying fetal hydrops due to a cardiac anomaly or intrauterine growth restriction, did not alter the diagnosis of an isolated cardiac defect. We excluded cases with a postnatal diagnosis of conditions considered physiological in fetal life, such type II atrial septal defects and isolated persistent arterial duct. Small ventricular septal defects or defects that were not visible in second trimester were not included in this study. Cases without an underlying structural heart defect such as cardiomyopathies or arrhythmias were excluded. Finally, unconfirmed heart defects after birth or autopsy were excluded.

### Outcome measures and statistical analysis

Primary outcome was the overall prenatal detection rate for isolated severe CHDs, including the prenatal detection rate before 24 weeks of gestation, and the GA at detection. Secondary outcomes were pregnancy outcomes, including live births and cases alive after 1 year of follow up, TOP, and intrauterine fetal death. Additionally, we evaluated GA at TOP. We calculated the rate

of each outcome measure for all CHD cases, and for the group with a first- and second-trimester scan (group 1) and the group with only a second-trimester scan (group 2), separately, expressed as a number with percentage, mean with standard deviation (SD) or median with interquartile range (IQR) when appropriate. A chi-square test was used to test associations between categorical variables. For dichotomous outcomes, differences between the groups were tested using the z-test for the difference in two (independent) proportions. Confidence intervals were also calculated. Numerical variables were studied for significant differences using the Mann-Whitney U test. We considered  $p < 0.05$  to be statistically significant. Statistical analyses were done using IBM Corp SPSS Statistics version 25.0 (IBM, Armonk, NY, USA) and RStudio version 1.2.1335.<sup>32</sup>

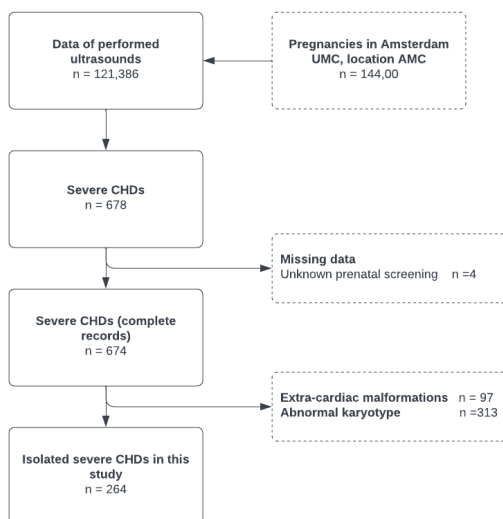
## Results

### Inclusions and prevalence of severe CHDs

We identified 678 fetuses with severe CHDs. We excluded 4 cases from further analyses because of missing data, 97 cases because of an extra-cardiac malformation and 313 with a chromosomal anomaly. Thus 264 cases with isolated severe CHDs were eligible for further analysis in this study (Figure 1).

The Amsterdam region covers 16,000 pregnancies annually, a total of 144,000 pregnancies during the 9-year study period. From 144,000 women, ultrasound evaluations were performed in 121,386 (84.3%) subjects, 61,255 combining first- and second trimester scans, and 60,131 with only second-trimester scans. For all 674 cases of severe CHDs, including cases with extra-cardiac malformations and abnormal karyotypes, the overall prevalence was 5.6 per 1,000 pregnancies. For isolated severe CHDs, that is 264 cases, the prevalence was 2.2 per 1000 pregnancies.

**Figure 1.** Flow chart summarizing the included isolated severe CHD cases





**Table 1.** Characteristics of study population in terms of type of isolated severe CHD\*, time of diagnosis and pregnancy outcome

Parameter	Total (n=264*)	Group 1	Group 2	Group 1 versus Group 2
		First- and second trimester scan (n=151)	Second trimester scan (n=113)	p-value
Type of isolated severe CHD				
1. Aortic arch anomalies	30 (11.4)	12 (7.9)	18 (15.9)	<0.05
2. Complex defects with atrial isomerism	12 (4.5)	10 (6.6)	2 (1.8)	0.06
3. Conotruncal anomalies	91 (34.5)	48 (31.8)	43 (38.1)	0.29
4. Hypoplastic left heart syndrome	28 (10.6)	16 (10.6)	12 (10.6)	1.00
5. Hypoplastic right heart syndrome	4 (1.5)	1 (0.7)	3 (2.7)	0.19
6. Other univentricular heart defects	32 (12.1)	21 (13.9)	11 (9.7)	0.30
7. Pulmonary venous return anomalies	6 (2.3)	2 (1.3)	4 (3.5)	0.23
8. Septal defects	38 (14.4)	26 (17.2)	12 (10.6)	0.14
9. Valvular anomalies	23 (8.7)	15 (9.9)	8 (7.1)	0.42
Time of diagnosis				
for total study population and for Group 1 (first and second trimester scan) and Group 2 (second trimester scan)				
Prenatal	172 (65.2)	106 (70.2)	66 (58.4)	<0.05
Prenatal <24 weeks of gestation	165 (62.5)	99 (65.6)	66 (58.4)	0.23
Prenatal <18 weeks of gestation	33 (12.5)	33 (21.8)	0 (0.0)	<0.0001
Prenatal <14 weeks of gestation	20 (7.6)	20 (13.2)	0 (0.0)	<0.0001
Postnatal	92 (34.8)	45 (29.8)	47 (41.6)	<0.05
Pregnancy outcome				
Live births	185 (70.1)	94 (62.2)	91 (80.5)	<0.01
Alive after 1 year of follow up	160 (86.5)	83 (88.3)	77 (84.6)	0.46
TOP	66 (25.0)	48 (31.8)	18 (15.9)	<0.01
IUFD	13 (4.9)	9 (6.0)	4 (3.5)	0.37

Data are given as n or n (%). TOP, termination of pregnancy, IUFD, intrauterine fetal death.

Categories per type of CHD consist of

1. Aortic coarctation, hypoplastic or interrupted aortic arch, double aortic arch;
2. Left or right atrial isomerism;
3. Tetralogy of Fallot, double outlet right ventricle-Fallot type (DORV) and ventricular septal defect (VSD) and/or pulmonary stenosis, simple transposition of great arteries (without significant VSD), complex TGA (with significant VSD and/or PS), DORV Taussig Bing (=TGA type), truncus arteriosus, pulmonary atresia with VSD, congenitally corrected TGA, absent pulmonary valve syndrome, aorta pulmonary window, hemitruncus, crisscross with TGA;
4. Aortic valve atresia or critical aortic valve stenosis with mitral atresia or mitral stenosis and left ventricular hypoplasia;
5. Pulmonary atresia with intact ventricular septum, critical pulmonary valve stenosis with right ventricular hypoplasia;
6. Double inlet left ventricle (DILV), tricuspid valve atresia, absent left A-V connection or mitral atresia, unbalanced atrioventricular septal defect, TGA with RV hypoplasia, DORV with mitral valve stenosis and LV hypoplasia, congenitally corrected TGA with RV hypoplasia, DILV with TGA and AVSD. isolated AV discordance with hypoplastic RV and VSD;
7. Total or partial abnormal pulmonary venous return;
8. Ventricular septal defect(s), balanced atrioventricular septal defect;
9. Pulmonary or aortic valve stenosis, Ebstein's anomaly, tricuspid dysplasia, tricuspid or mitral regurgitation, unguarded tricuspid valve orifice with UHls anomaly, pulmonary atresia and VSD.

\*Type of isolated severe CHD was based on postnatal diagnosis in 84.5% (223/264).

### Spectrum and groups of isolated severe CHDs

Table 1 presents an overview of the characteristics of the included cases. Of the 264 cases, 57.1% (151/264) received both a first- and second trimester anomaly scan (group 1) and 42.8% (113/264) solely had a second-trimester anomaly scan (group 2). The first-trimester scans were done as part of FCT in 61.6% (93/151), 25.8% (39/151) were dating scans and 12.6% (19/151) were NT measurements. A NT measurement was obtained in 74.2% of all first-trimester scans (112/151) and 18.8% (21/112) had an increased NT ( $\geq 3.5$  mm). The majority of these cases, that is 76.2% (16/21), underwent invasive diagnostics. Conotruncal anomalies (34%, 91/264) and septal defects (14%, 38/264) were the most frequently detected heart defects in this cohort. This was similar amongst the two groups, except for aortic arch anomalies, which were more prevalent in group 2 (Table 1). There was a trend towards more complex heart defects in group 1 ( $p = 0,06$ ).

### Prenatal detection rate over time

Prenatal detection rate of all CHDs did not change significantly over the years with 62.7% (94/150) in 2007-2011 compared to 68.4% (78/114) in 2012-2015 ( $p=0.33$ ). Prenatal detection rate before 24 weeks gestation was 59% ( $n=88/150$ ) in 2007-2011 compared to 68% ( $n= 77/114$ ) in 2012-2015 ( $p=0.14$ ). Prenatal detection before 24 weeks of conotruncal anomalies increased from 58.8% (30/51) in 2007-2011 to 70% (28/40) ( $p=0.27$ ). Similarly, the prenatal detection of aortic arch anomalies increased from 17.6% (3/17) versus 53.8% (7/13) in 2012-2015 ( $p=0.04$ ).

### Prenatal detection rate of isolated severe CHDs

The prenatal detection for all isolated CHD cases was 65.2% (172/264, 95% CI: 59.1-70.9). Of the total, 63% (165/264, 95% CI: 56.4-68.4) were detected before 24 weeks of gestation (Table 1). The highest prenatal detection rates were found in hypoplastic left heart syndrome (HLHS) (96.4%, 27/28), other univentricular defects (96.9%, 31/32) and complex heart defects with atrial isomerism (100%, 12/12). Pulmonary venous return anomalies (0%, 0/6), aortic arch anomalies (36.7%, 11/30) and ventricular septal defects (34.2%, 13/38) were most frequently missed.

The prenatal detection rate in group 1 was 70.2% (106/151) compared to 58.4% (66/113) in group 2 (difference 11.8%, 95% CI: 0.14 – 23.4,  $p<0.05$ ) (Table 1). The detection rate before 24 weeks of gestation was 65.6% for group 1 (99/151) versus 58.4% (66/113) for group 2 (difference 7.2%, 95% CI: -4.7 – 19.0,  $p=0.23$ ). Prenatal detection rate before 14 weeks of gestation was 13.2% (20/151, 95% CI: 8.3 – 19.7) in group 1 (Table 1). Of the cases in group 1, 21.8% (33/151, 95% CI: 15.5 – 29.3) were diagnosed before 18 weeks, thus 12.5% (33/264) of the total cohort were diagnosed before 18 weeks. Of the cases detected before 14 - and 18 weeks of gestation, 50% (10/20) and 42% (14/33) respectively, had an increased NT.

In group 1, 4.6% (7/151) of CHD cases were detected after 24 weeks of gestation compared to 0% (0/113) in group 2. These included valvular anomalies (n=2), transposition of the great arteries (n=1), coarctation of the aorta (n=1), pulmonary valve stenosis (n=1), and ventricular septal defects (n=2). An overview of the prenatal detection rate per type of CHD for the two groups is presented in Table 2. Although the prenatal detection rate was higher in group 1 for certain types of CHDs the differences were not statistically significant (Table 2).

Table 3 presents median GA at detection before 24 weeks, stratified per group and type of CHD. The median gestational GA at detection before 24 weeks was 19+6 (IQR, 15+4 - 20+5) in Group 1 versus 20+3 (IQR, 20+0 - 21+2) in group 2 ( $p < 0.001$ ). Septal defects and other univentricular heart defects were diagnosed earlier in group 1 compared to group 2 ( $p < 0.05$ ) (Table 3).

**Table 2.** Prenatal detection per category of CHD compared between group 1 and group 2

Type of isolated severe CHD	Group 1		Group 2		Difference in prenatal detection	p-value
	First- and second trimester scan		Second-trimester scan			
	Total (n)	Prenatal detection (%)	Total (n)	Prenatal detection (%)	95% CI	
1. Aortic arch anomalies	12	50.0	18	27.8	22.2 (-12.9-57.2)	0.22
2. Complex defects with atrial isomerism	10	100.0	2	100.0	0.0	NA
3. Conotruncal anomalies	48	66.7	43	62.8	4.0 (-15.8-23.5)	0.69
4. Hypoplastic left heart syndrome	16	100.0	12	91.7	8.3 (-7 -23.9)	0.24
5. Hypoplastic right heart syndrome	1	100.0	3	66.7	33.3 (-20-86.7)	0.51
6. Other univentricular heart defects	21	95.2	11	100.0	4.8 (-4.3-13.9)	0.46
7. Septal defects	26	38.5	12	25.0	14.0 (-17.4-44.3)	0.42
8. Valvular anomalies	15	73.3	8	62.5	10.8 (-29-51.1)	0.59
9. Venous return anomalies	2	0.0	4	0.0	0.0	NA
Total	151	70.2	113	58.4	11.8 (0.14-23.4)	<0.05

Data are given as n (%). CHD, congenital heart defect; CI, Confidence interval; NA, not applicable.

**Table 3.** Prenatally diagnosed cases before 24 weeks of gestation sorted by type of CHD compared between groups 1 and 2

Type of isolated severe CHD	Group 1		Group 2		p-value
	First- and second trimester scan		Second-trimester scan		
	n	GA at detection	n	GA at detection	
1. Aortic arch anomalies	5	21 <sup>+4</sup> (16 <sup>+5</sup> – 22 <sup>+0</sup> )	5	20 <sup>+4</sup> (19 <sup>+6</sup> – 22 <sup>+1</sup> )	0.841
2. Complex defects with atrial isomerism	9	15 <sup>+6</sup> (13 <sup>+3</sup> – 18 <sup>+2</sup> )	2	20 <sup>+6</sup> (20 <sup>+3</sup> – 20 <sup>+6</sup> )	0.073
3. Conotruncal anomalies	31	20 <sup>+3</sup> (19 <sup>+5</sup> – 21 <sup>+1</sup> )	27	20 <sup>+4</sup> (20 <sup>+0</sup> – 21 <sup>+3</sup> )	0.271
4. Hypoplastic left heart syndrome	16	20 <sup>+0</sup> (14 <sup>+6</sup> – 20 <sup>+3</sup> )	11	20 <sup>+3</sup> (19 <sup>+6</sup> – 21 <sup>+3</sup> )	0.064
5. Hypoplastic right heart syndrome	1	17 <sup>+2</sup> (NA)	2	20 <sup>+6</sup> (20 <sup>+4</sup> – 20 <sup>+6</sup> )	NA
6. Other univentricular heart defects	19	19 <sup>+0</sup> (15 <sup>+3</sup> – 20 <sup>+4</sup> )	11	20 <sup>+2</sup> (20 <sup>+1</sup> – 21 <sup>+0</sup> )	<0.05
7. Septal defects	9	13 <sup>+4</sup> (12 <sup>+1</sup> – 19 <sup>+6</sup> )	3	21 <sup>+1</sup> (20 <sup>+3</sup> – 21 <sup>+1</sup> )	<0.05
8. Valvular anomalies	9	19 <sup>+6</sup> (13 <sup>+5</sup> – 21 <sup>+3</sup> )	5	20 <sup>+0</sup> (19 <sup>+4</sup> – 20 <sup>+5</sup> )	0.699
9. Venous return anomalies	0	NA	0	NA	NA
Total	99	19 <sup>+6</sup> (15 <sup>+4</sup> – 20 <sup>+5</sup> )	66	20 <sup>+3</sup> (20 <sup>+0</sup> – 21 <sup>+2</sup> )	<0.001

Data are given as median (IQR). GA, gestational age; NA, not applicable.

### Pregnancy outcome overall

In total, 70.1% (185/264) of CHD cases were live born, in 25% (66/264) the pregnancy was terminated and in 4.9% (13/264) the pregnancy ended in a spontaneous miscarriage or intrauterine fetal death (Table 1). Of the live born, 86.5% (160/185) were alive one year after follow-up. Consequently, the first year mortality was 13.5% (25/185) of which 52% (13/25) died in the neonatal period and 48% (12/25) thereafter. CHDs that were most likely to survive after one year of follow-up were aortic arch anomalies (25/30, 83.3%), conotruncal anomalies (70/91, 76.9%) and septal defects (29/38, 76.3%). The overall TOP rate was 25% (66/264, 95% CI: 19.8 – 30.7). TOP rates were highest for hypoplastic left heart syndrome (HLHS) and other univentricular heart defects, 64.2% (18/28, 95% CI: 44.1 – 81.4) and 46.9% (15/32, 95% CI: 29.1 – 65.3) respectively.

### Pregnancy outcome separated per group

In group 1, 88.3% (83/94) of the live born children were alive one year after follow-up compared to 84.6% (77/91) in group 2 (difference: 3.7 95% CI: -0.6 – 13.5 p=0.46) (Table 1). Consequently, the first-year mortality was 11.7% (11/94) in group 1, compared to 15.4% (14/91) in group 2 (difference: 3.7%, p =0.46).

In cases diagnosed before 24 weeks of gestation, the TOP rate was 48.5% (48/99) in group 1 versus 27.2% (18/66) in group 2 (difference: 21%, 95% CI: 6.7 – 35.8, p<0.01) (Table S1). The TOP rate for HLHS was 75.0% (12/16) in group 1 versus 54.5% (6/11) in group 2 (difference 20.5%, 95% CI: -15.8 – 56.7 p=0.27). The TOP rate for univentricular heart defects was 57.9% (11/19) in group 1 compared to 36.3% (4/11) in group 2 (difference 21.6%, 95% CI: -14.5 – 57.6 p=0.26) (Table S1).

In group 1, the TOP rate was highest when a diagnosis was made before 18 weeks of gestation (33 cases), as 69.7% (23/33, 95% CI: 51.2 – 84.4) of parents opted for a TOP with a median GA of 13+3

(IQR, 12+1 – 15+4). Before 18 weeks of gestation, a TOP was performed in all cases of HLHS (5/5) and hypoplastic right heart (1/1) and in 71.4% of cases with univentricular heart defects (5/7). Median GA of TOP in group 1 was 21+3 (IQR, 16+6 – 22+6) compared to 22+1 (IQR, 21+2 – 22+4) in group 2 ( $p=0.121$ ). Median GA did not differ among different types of CHDs (Table S2).

## Discussion

### Main findings

In this study, we confirmed that an additional first-trimester scan plays a crucial role in the detection of isolated severe CHDs and has impact on prenatal detection rate and pregnancy outcome. In women with both a first-and second-trimester scan, the prenatal detection rate was 70.2% compared to 58.4% if only a second-trimester scan was performed. The termination of pregnancy rate was also higher in this group, but this did not result in a difference in timing of terminating a pregnancy. Given the fact that the more serious CHD cases (univentricular heart defects) were detected and terminated in first-trimester, the number of live births after one year of follow-up were comparable between the two groups.

### Interpretation

The implementation of secondary trimester screening programs by governments in high income countries with the evaluation of the fetal heart, has resulted in a gradual increase in the prenatal detection of isolated CHDs.<sup>7,11,33</sup> We found a remarkably high prenatal detection rate of more than 65% in isolated severe CHD cases. Of these prenatally detected cases, more than 95% were detected before 24 weeks of gestation. The high prenatal detection rate in our study is likely the result of the national screening program in the Netherlands, with a uniform protocol for the second-trimester scan and regulations regarding training and quality monitoring of sonographers.<sup>34,35</sup> Secondly, there was a significant change in the Dutch protocol in 2012, when the 3W was added as a mandatory plane for fetal heart screening in second-trimester.<sup>18</sup> The addition of this obligatory plane has been highly beneficial in the detection of outflow tract anomalies.<sup>18</sup>

First-trimester anomaly screening starts to play a crucial role in pregnancy management given the detection of major congenital anomalies before 14 weeks of gestation.<sup>36</sup> It has been previously suggested that an increased NT  $\geq 3.5$  mm may have contributed to the early detection of severe congenital CHD. Moreover, CHDs can also be suspected in the first-trimester when a combination of an increased NT, a reversed a-wave in the ductus venosus Doppler and tricuspid regurgitation is used.<sup>37,38</sup> Unfortunately, even when combined, these markers have shown a low sensitivity for the detection of CHDs.<sup>39-41</sup> In our total cohort, 19% of CHD cases with a first-trimester scan had an increased NT  $\geq 3.5$  mm. Of the CHD cases detected before 14 weeks of gestation, 50% were associated with an increased NT, thus emphasizing the importance of first-trimester markers.

Moreover, since fetuses with an increased NT also received an additional ultrasound scan around 30 week of gestation, 7 late diagnoses were made in the group with a first-trimester scan compared to 0 in the group with only a second-trimester scan. 71.4% of these late diagnoses were CHDs more likely to be detected later in pregnancy or are unlikely to have immediate postnatal consequences (e.g. coarctation of the aorta or valve lesions).<sup>26</sup> This is comparable to other studies.<sup>17</sup> Although NT measurement alone may not be sensitive enough to use for CHD screening, our results indicate that our current policy should be preserved. Women carrying a fetus with an increased NT should be referred to a Fetal Medicine Unit for advanced ultrasound examination. Furthermore, they should receive an additional ultrasound around 30 weeks of gestation.

The most important benefit of an additional first-trimester scan is the earlier gestational age at detection. This plays a pivotal role to allow expectant parents to contemplate and to make educated decisions about perinatal management. It provides the opportunity to perform chromosomal analysis and whole exome sequencing (WES), the current high standard test, given the association of CHDs with genetic syndromes.<sup>20</sup> Additionally, it gives sufficient time for counseling by a multidisciplinary team not only about the specific type of CHD and the effect on the health of the fetus, but also time to explore the consequences of this finding on the well-being of the parents and potential siblings. Moreover, it allows for a planned delivery in a center able to provide optimal postnatal care (neonatal intensive care, pediatric and pediatric cardiothoracic surgical facilities). On the other hand it also gives parents the freedom to make autonomous reproductive choices and the opportunity to decide whether they wish to continue the pregnancy and prepare for medical procedures after birth, or opt for termination of the pregnancy.

In our study, the higher prenatal detection rate for cases with an additional first-trimester scan was accompanied by a two-fold higher TOP rate before 24 weeks of gestation. We found a TOP rate of 70% in cases detected before 18 weeks, with parents opting for TOP in almost all cases with univentricular heart defects. We hypothesize that since most of the scans were performed in parents undergoing FCT, they could have had a different attitude towards TOP as opposed to those who did not want first-trimester screening. Surprisingly, despite the higher TOP rate among the group with a first-trimester scan, the gestational age of TOP was similar among groups. The explanation for this may be two-fold. On the one side the physician's insecurity of the final diagnosis at an early gestational age may have played a role. This is illustrated by the fact that parents with a first-trimester diagnosis had three scans before TOP as compared to only two scans in those with a second-trimester diagnosis. Alternatively, the extra scan might also be a reflection of parental insecurity with an early diagnosis, necessitating an additional examination to illustrate the defect in a larger fetus. It has been demonstrated that earlier TOP may be associated with significant psychological and physical benefits for the mother compared to a later termination.<sup>42</sup> Although the first-trimester anomaly scan seems promising, the accuracy of diagnosis in the first-

trimester depends on the experience of the sonographer, the studied population and the type of CHD.<sup>26,43</sup> Several studies reported heterogeneous detection rates ranging from 10% or less<sup>43,44</sup> to 34% in the largest study performed<sup>12</sup>, which is comparable to the 13% prenatal detection rate before 14 weeks in our study. First-trimester detection of CHD varies widely between different types of cardiac anomalies. This is demonstrated by the prenatal detection rate of more than 95% of right/left hypoplastic heart syndrome, other univentricular heart defects and conotruncal anomalies in our study. A recent meta-analysis detected showing that over half (56%) of fetuses affected by major cardiac pathology<sup>45</sup> are detected in first trimester confirms this finding. It is hypothesized that if a structured protocol is followed with assessment of outflow tract views and color-flow Doppler imaging, detection rates will improve.<sup>45,46</sup> Another limitation emphasized by several studies is the high false positive rate in first trimester, since an anomaly identified in first trimester may evolve or may be reclassified later in pregnancy.<sup>45</sup>

### Strengths and limitations

This study represents a large cohort of isolated severe CHDs, from a population of 121,386 pregnancies. The birth prevalence of isolated severe CHD in our cohort was 2.2 per 1000 pregnancies, this is consistent with previous reported figures.<sup>2,17,34</sup> Another strength of this study is that it is a geographical cohort study, representing all isolated severe CHD cases in the Amsterdam region. We ascertained that all children with a severe CHDs were enrolled in the CAHAL database, by combining several local databases in the Amsterdam-Leiden region. We reviewed all included isolated severe CHD cases with a paediatric cardiologist to ensure correct and uniform classification of the heart diagnoses. Where previous cohort studies emphasized markers in first-trimester for early detection of CHDs<sup>26</sup>, and reported that the spectrum of CHDs diagnosed in first and second-trimester differs<sup>47</sup>, this is the first study that has evaluated the additional value of a first-trimester scan with regards to the time of diagnosis and pregnancy outcome in isolated severe CHDs.

There are some caveats that need to be considered in the interpretation of our data. The first limitation is the retrospective design of the study. It is a descriptive cohort which implies that no causality but only associations can be demonstrated based on this data. Another import limitation is that the first-trimester scan was not performed routinely in this population. The main goal of the first-trimester scan was to screen for aneuploidy, with CRL and mostly NT measurement as the only mandatory measurements. As a result, women at high risk for adverse pregnancy outcomes may be overrepresented. In addition, the first-trimester ultrasound was not part of a national screening program with a fixed protocol, there the heart was not structurally assessed. We did exclude chromosomal anomalies but did not excluded fetuses with increased NT. Selection bias could have occurred since pregnant women with an increased NT were referred to a Fetal Medicine Unit for a detailed anomaly scan, possibly leading to earlier detection of CHDs. Another limitation is that

outcome measures are limited. Since we only could report on first-year survival, the impact of an early prenatal diagnosis on long-term cardiac- or neurological outcome and quality of life is unknown.

## **Conclusion**

An additional first-trimester scan provides the opportunity to examine the fetal heart at an earlier gestation. To achieve optimal results, it is imperative that trained and experienced sonographers perform a first-trimester scan, according to a structured protocol. It should not replace a second-trimester anomaly scan and parents should be made aware that a more accurate detection and prediction of fetal outcome is achievable at a later stage. Our results demonstrate that an additional first-trimester scan could result in a higher prenatal detection rate of isolated severe CHDs and affect gestational age at diagnosis and pregnancy outcome. Early diagnosis leads to more willingness among expectant parents to terminate the pregnancy, but has no effect on the timing of TOP.



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## Supplemental material

*Table S1.* TOP rate of prenatally diagnosed cases before 24 weeks of gestation sorted by type of CHD compared between Group 1 and 2

*Table S2.* Gestational age of TOP sorted by type of CHD compared between Group 1 and 2

