CHAPTER 3

Prenatal Detection of Congenital Heart Disease: Results of a National Screening Programme


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Letter

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Reply

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ABSTRACT

Objective
Congenital heart disease (CHD) is the most common congenital malformation and causes major morbidity and mortality. Prenatal detection improves the neonatal condition before surgery, resulting in less morbidity and mortality. In the Netherlands a national prenatal screening programme was introduced in 2007. This study evaluates the effects of this screening programme.

Design
Geographical cohort study.

Setting
Large referral region of three tertiary care centres.

Population
Fetuses and infants diagnosed with severe CHD born between 1 January 2002 and 1 January 2012.

Methods
Cases were divided into two groups: before and after the introduction of screening.

Main outcome measures
Detection rates were calculated.

Results
The prenatal detection rate (n = 1912) increased with 23.9% (95% confidence interval [95% CI] 19.5–28.3) from 35.8 to 59.7% after the introduction of screening and of isolated CHD with 21.4% (95% CI 16.0–26.8) from 22.8 to 44.2%. The highest detection rates were found in the hypoplastic left heart syndrome, other univentricular defects and complex defects with atrial isomerism (>93%). Since the introduction of screening, the ‘late’ referrals (after 24 weeks of gestation) decreased by 24.3% (95% CI 19.3–29.3).

Conclusions
This is the largest cohort study to investigate the prenatal detection rate of severe CHD in an unselected population. A nationally organised screening has resulted in a remarkably high detection rate of CHD (59.7%) compared with earlier literature.
INTRODUCTION

Congenital heart disease (CHD) is the most common congenital malformation and affects approximately 6–11 per 1000 newborns.\textsuperscript{1-4} About 20–30\% of these heart defects are severe, defined as being potentially life threatening and requiring surgery within the first year of life.\textsuperscript{2,5-7} Only 10\% of CHD cases occur in pregnancies with identifiable risk factors, such as fetal extracardiac malformations.\textsuperscript{8,9} The current screening strategy in most western countries is a standard anomaly scan at 20 weeks of gestation.\textsuperscript{8} Although the prenatal detection rate of CHD has improved in the last decades,\textsuperscript{5,10} the reported detection rate in low-risk populations does not exceed 35–40\%.\textsuperscript{7,10-14} Prenatal detection of specific types of CHD may reduce neonatal mortality and morbidity.\textsuperscript{15-19} It allows for planning the delivery at a tertiary-care centre ensuring optimal neonatal and perisurgical care. Furthermore, parents can consider termination of pregnancy (TOP) in severe cases.\textsuperscript{20-22} In the Netherlands in January 2007 a nationwide screening programme, with the aim to detect congenital anomalies, was introduced. Before 2007 fetal ultrasound was exclusively performed for the evaluation of obstetric complications during pregnancy or in pregnancies with an increased risk of fetal abnormalities (first- or second-degree family member with CHD or other congenital anomalies). The defined and uniform introduction of the national standard anomaly scan for all pregnant women provided the unique opportunity to study the effect of such a programme. The primary aim of this study was to evaluate the effectiveness of the national screening programme on the prenatal detection of severe CHD in an unselected population in the Netherlands. The secondary aims were to assess the gestational age at prenatal diagnosis and to study the effect of the screening programme on the mortality rates.

METHODS

Region and referral system

This was a geographical cohort study, conducted in the northwest region of the Netherlands. In this area 72 000 infants are born per year, which is approximately 40\% of all live births in the Netherlands. Three tertiary referral centres, Academic Medical Centre Amsterdam, VU Medical Centre Amsterdam and Leiden University Medical Centre Leiden, are responsible for the care of children with CHD in this region. All infant cardiothoracic surgery is performed in the Leiden University Medical Centre. This collaboration is called the CAHAL (Centre for congenital heart defects Amsterdam and Leiden—in Dutch Centrum voor Aangeboren Hartafwijkingen Amsterdam-Leiden). Prenatal screening in the Netherlands is mostly performed in primary and secondary healthcare centers by ultrasonographers and obstetricians (performing respectively 96\% and 4\% of the standard anomaly scans). Only the women with an increased risk
of having offspring with a congenital anomaly are screened in tertiary centres. All ultrasonographers are educated and are required to take a practical and a theoretical examination according to the Fetal Medicine Foundation criteria. Furthermore, they are required to conduct at least 150 structural anomaly scans per year. Every 2 years the quality of their scans is assessed by regional surveillance committees. The standard anomaly scan is performed between 18 and 22 weeks gestational age according to a national protocol. The assessment of the fetal heart in the Dutch anomaly scan entailed the assessment of the four-chamber view (size of the heart and position in thorax, symmetry of the atria and ventricles, identification of atrophicventricular valves and crux) and the right and left outflow tract views. The assessment of the three-vessel view (a transverse section of the fetal thorax, just above the level of the four-chamber view) was only made compulsory from January 2012, once the ultrasonographers’ cardiac scanning experience had increased. The three-vessel view depicts the spatial relationship of the aorta and pulmonary artery and is beneficial in the detection of outflow tract anomalies. In case a congenital (heart) defect is suspected, the woman is referred to one of the tertiary centres. In the tertiary centres fetal echocardiography is performed by a specialised perinatologist in collaboration with a paediatric cardiologist. After a prenatal diagnosis of CHD, karyotyping was routinely recommended.

Cases
We included all cases with a prenatal or postnatal diagnosis of severe CHD born between 1 January 2002 and 1 January 2012, irrespective of presence or absence of additional congenital anomalies. For inclusion the mother of the fetus or the infant had to be resident within the study region at the time of birth. Severe CHD was defined as being potentially life threatening and requiring surgery or intervention within the first year of life. All cases with severe abnormal cardiac findings in the pregnancy (including pregnancies with fetal demise or TOP) were identified in the prenatal ultrasound databases of the tertiary centres. Fetal cases were prospectively entered in these databases. The case list was complemented with all postnatally diagnosed infants with a CHD who needed surgery or therapeutic cardiac catheterisation or who died within the first year of life. They were selected from the paediatric cardiology departmental databases and cross-checked with catheterisation schedules, operating schedules and emergency admissions. The postnatal cases were prospectively entered in the paediatric departmental databases. The postmortem databases of the departments of pathology were studied for cardiac anomalies, to identify cases in which death had occurred outside a hospital or in which the child was dead on arrival at an emergency room. Finally, the database of the Dutch sudden infant death syndrome registry was searched for all cardiac causes that may not have been recorded in the hospital databases. All the cases were reviewed and the
prenatal and postnatal data were matched. To assess the effectiveness of the national screening programme on the prenatal detection of CHD, data from the period 2002–2006 were compared with data from 2007 to 2011. Cases of isolated fetal or neonatal arrhythmia were not included. We excluded isolated secundum atrial septal defects and/or isolated persistent arterial ducts as these conditions are normal in fetal life. In the Netherlands, by participating in prenatal screening, pregnant women automatically give consent to use the anonymised data of the pregnancy and the outcome for research. Approval from the Medical Ethical Committee of the VU University Medical Centre was obtained for this study. This study complies with the Declaration of Helsinki.

Data collection
Data concerning the mother, pregnancy, birth and infant were collected from medical files. The gestational ages at both referral and diagnosis were retrieved. The final prenatal cardiac diagnosis was recorded. In cases in which data about prenatal screening were missing, infants born after 1 May 2007 were considered screened prenatally (since the national screening programme was introduced on 1 January 2007). The postnatal echocardiography, surgical report, autopsy or magnetic resonance imaging determined the definitive diagnosis in the analysis of the data. The postnatal diagnoses were coded and categorised as depicted in Table 1. In cases with more than one cardiac diagnosis the most important heart anomaly (in terms of determining the prognosis) of the fetus or infant was stated (for example a coarctation of the aorta combined with a ventricular septal defect [VSD] was coded as a coarctation). We defined heart defects as univentricular, when in postnatal life the heart could only be surgically managed as a single ventricle. In cases in which a postnatal diagnosis was not available (e.g. in some cases with TOP or intrauterine fetal death without a postmortem), the prenatal diagnosis was used to categorise the heart defect. The presence of extracardiac congenital anomalies, either as a prenatal or a postnatal finding, was recorded. Prenatally detected extracardiac anomalies were categorised as: single or multiple extracardiac structural anomaly/ies, intrauterine growth restriction, oligohydramnios or polyhydramnios, fetal hydrops and nuchal translucency >3.5 mm. Prenatally detected aneuploidy and genetic syndromes were also recorded. Postnatally diagnosed congenital anomalies were categorised as: aneuploidy, confirmed genetic syndrome, multiple or single extracardiac anomaly/ies. Isolated CHD was defined as CHD without any other congenital anomalies (except single umbilical artery).

Statistical analysis
The prenatal detection rate of CHD in the years before introduction of the screening programme was estimated at 20%, a little higher than the last Dutch data published in
1996 (16.7%). After the introduction we anticipated a detection rate of around 40% according to earlier published international studies with comparable programmes. A sample size of 300 cases was necessary to show a significant difference in detection rate (power 90% and α = 0.01). Comparisons were made between the group before and after introduction of the national screening programme. A chi-square test was used to test associations between categorical variables, the Student’s t test was used to test differences between numeric variables. For dichotomous outcomes, differences between the groups were tested using the two-sample z-test for proportions. Confidence intervals were also calculated. We considered P values <0.05 as statistically significant; all tests were two-sided. We corrected for multiple testing by using Bonferroni correction, in other words for each subgroup of outcome measures the P value was adjusted by dividing the P value of 0.05 by the number of tests. Data analysis was generated using SPSS software (version 20; SPSS Inc., Chicago, IL, USA).

**RESULTS**

**Inclusions and follow up**

In total, 1965 cases were eligible for inclusion in the study. Fifty-three cases were excluded from further analysis for the following reasons; date of birth in 2012 or postnatal cases with the first cardiac surgery after the age of 12 months. This resulted in 1912 inclusions. In the study period 1413 infants were liveborn with a severe CHD in this region. The total live birth rate in this period in the same region was 720 138 (data supplied by Statistics Netherlands, CBS), resulting in a live birth prevalence for severe CHD of 2.0 per 1000 in this region. Overall, the total birth (including stillbirth and termination of pregnancy) prevalence of severe CHD was 2.7 per 1000 births. A flow chart of the inclusions and follow up is shown in Figure 1. Follow up of all cases was at least 1 year after birth. Only 0.3% of the cases was lost to follow-up (two cases without information on pregnancy outcome and four cases lacking information on first-year mortality). The lost-to-follow-up cases were all included in the analysis.

**Prenatal detection of CHD**

An overview of the prenatal detection rate of categorised groups of CHD in our cohort is shown in Table 1. The detection rate of all CHD increased significantly from 35.8% before to 59.7% after the introduction of the national screening programme (P < 0.001). The detection rate of isolated CHD increased from 22.8 to 44.2% (P < 0.001). The highest prenatal detection rates after introduction of screening were found in hypoplastic left heart syndrome, other univentricular defects and the complex heart defects with atrial isomerism (>93%).
An overview of the prenatal detection of specific diagnosis of CHD—with a number large enough to present results—are shown in Table 2. Significant improvements were made in the prenatal detection of hypoplastic left heart syndrome, coarctation of the aorta, double outlet right ventricle with VSD and pulmonary stenosis (DORV-Fallot), transposition of the great arteries with intact ventricular septum (TGA), truncus arteriosus and pulmonary atresia with VSD.
### Table 1 Prenatal detection per category of congenital heart disease before and after introduction of the screening program

<table>
<thead>
<tr>
<th>Heart defect category</th>
<th>Before introduction of screening</th>
<th>After introduction of screening</th>
<th>Difference in prenatal detection (% 95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n)</td>
<td>Prenatal detection (%)</td>
<td>Total (n)</td>
<td>Prenatal detection (%)</td>
</tr>
<tr>
<td>1. Septal defects</td>
<td>272</td>
<td>37.1</td>
<td>230</td>
<td>50.4</td>
</tr>
<tr>
<td>2. Valvular anomalies, biventricular heart</td>
<td>65</td>
<td>20.0</td>
<td>65</td>
<td>32.3</td>
</tr>
<tr>
<td>3. Venous return anomalies</td>
<td>23</td>
<td>4.3</td>
<td>27</td>
<td>11.1</td>
</tr>
<tr>
<td>4. Aortic arch anomalies</td>
<td>117</td>
<td>12.0</td>
<td>91</td>
<td>29.7</td>
</tr>
<tr>
<td>5. Conotruncal anomalies</td>
<td>267</td>
<td>26.6</td>
<td>229</td>
<td>59.8</td>
</tr>
<tr>
<td>6. Hypoplastic Right Heart syndrome</td>
<td>22</td>
<td>50.0</td>
<td>18</td>
<td>66.7</td>
</tr>
<tr>
<td>7. Hypoplastic Left Heart syndrome</td>
<td>85</td>
<td>54.1</td>
<td>82</td>
<td>97.6</td>
</tr>
<tr>
<td>8. Other univentricular heart defects</td>
<td>83</td>
<td>57.8</td>
<td>78</td>
<td>94.9</td>
</tr>
<tr>
<td>9. Complex defects with atrial isomerism</td>
<td>31</td>
<td>64.5</td>
<td>31</td>
<td>93.5</td>
</tr>
<tr>
<td>10. Miscellaneous</td>
<td>48</td>
<td>20.8</td>
<td>48</td>
<td>20.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1013</td>
<td>35.8</td>
<td>899</td>
<td>59.7</td>
</tr>
<tr>
<td><strong>Isolated CHD</strong></td>
<td>619</td>
<td>22.8</td>
<td>527</td>
<td>44.2</td>
</tr>
</tbody>
</table>

Legend: p value (Bonferroni corrected) is considered significant if <0.005.

Categories consist of:

1. Ventricular septal defect(s), balanced atrioventricular septal defect
2. Pulmonary or aortic valve stenosis, mitral stenosis, Ebstein’s anomaly, tricuspid dysplasia, tricuspid or mitral regurgitation
3. Total or partial abnormal pulmonary venous return, giant eustachian valve/cor triatriatum dexter or sinister
4. Aortic coarctation, hypoplastic or interrupted aortic arch, multiple level left heart obstruction, double aortic arch
5. Tetralogy of Fallot, double outlet right ventricle-fallot type or DORV and 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, aortopulmonary window, hemitruncus
6. Pulmonary atresia with intact ventricular septum, critical pulmonary valve stenosis with right ventricular hypoplasia
7. Aortic valve atresia or critical aortic valve stenosis with left ventricular hypoplasia
8. Double inlet left ventricle, tricuspid valve atresia, absent left A-V connection, unbalanced AVSD, TGA with RV hypoplasia and straddling tricuspid valve, criss-cross, DORV with mitral valve and LV hypoplasia, congenitally corrected TGA with RV hypoplasia, isolated AV discordance with hypoplastic RV and VSD
9. Left or right atrial isomerism, heterotaxy syndromes
10. Cardiomyopathy, generalized arteriopathy, complex severe heart defect in aneuploidy other than trisomy 21, polyvalvular disease, isolated double chambered right ventricle, right atrial aneurysm, aortic root dilatation (Marfan)
### Table 2 Prenatal detection per type of severe CHD before and after introduction of the screening program

<table>
<thead>
<tr>
<th>Heart defect</th>
<th>Before introduction of screening</th>
<th>After introduction of screening</th>
<th>Difference in prenatal detection (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>167</td>
<td>136</td>
<td>10.3 (-0.4-21.0)</td>
<td>0.060</td>
</tr>
<tr>
<td><strong>Ventricular septal defect</strong></td>
<td>28.7</td>
<td>39.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Attrioventricular septal defect, balanced</strong></td>
<td>50.5</td>
<td>67.0</td>
<td>16.5 (3.0-30.0)</td>
<td>0.018</td>
</tr>
<tr>
<td><strong>Pulmonary valve stenosis</strong></td>
<td>8.0</td>
<td>19.2</td>
<td>11.2 (-7.3-29.7)</td>
<td>0.244</td>
</tr>
<tr>
<td><strong>Aortic valve stenosis</strong></td>
<td>8.7</td>
<td>26.9</td>
<td>18.2 (-2.4-38.8)</td>
<td>0.100</td>
</tr>
<tr>
<td><strong>Attrioventricular valve dysplasia/stenosis/ regurgitation</strong></td>
<td>47.1</td>
<td>69.2</td>
<td>17.6 (-12.4-56.6)</td>
<td>0.367</td>
</tr>
<tr>
<td><strong>Totally/partially abnormal pulmonary venous return</strong></td>
<td>9.1</td>
<td>10.0</td>
<td>0.9 (-16.9-18.7)</td>
<td>0.639</td>
</tr>
<tr>
<td><strong>Coarctation of aorta</strong></td>
<td>8.1</td>
<td>25.7</td>
<td>17.6 (5.9-29.3)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Tetralogy of Fallot</strong></td>
<td>22.2</td>
<td>41.7</td>
<td>19.5 (2.2-36.8)</td>
<td>0.028</td>
</tr>
<tr>
<td><strong>Double outlet right ventricle (Fallot-type)</strong></td>
<td>48.6</td>
<td>82.9</td>
<td>34.3 (14.1-54.5)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Transposition of great arteries, simple</strong></td>
<td>14.3</td>
<td>44.2</td>
<td>29.9 (12.5-47.3)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>TGA complex (with significant VSD and/or DORV or pulmonary stenosis)</strong></td>
<td>26.5</td>
<td>53.1</td>
<td>26.6 (3.8-49.4)</td>
<td>0.027</td>
</tr>
<tr>
<td><strong>Truncus arteriosus</strong></td>
<td>31.6</td>
<td>85.2</td>
<td>53.6 (28.5-78.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Pulmonary atresia with VSD (± main aortico-pulmonary collateral arteries)</strong></td>
<td>24.2</td>
<td>61.9</td>
<td>37.7 (12.3-63.1)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Tricuspid valve atresia</strong></td>
<td>55.0</td>
<td>88.2</td>
<td>33.2 (6.0-60.4)</td>
<td>0.028</td>
</tr>
<tr>
<td><strong>Unbalanced AVSD</strong></td>
<td>77.8</td>
<td>92.9</td>
<td>15.1 (-6.3-36.5)</td>
<td>0.138</td>
</tr>
</tbody>
</table>

Legend: All heart defects in this table required surgery or caused death.  
a p value (Bonferroni corrected) of <0.0033 was considered statistically significant.  
*Ebstein’s anomaly included.*
Aneuploidy and syndromes

The rates of aneuploidy, genetic syndromes, extracardiac anomalies and pregnancy outcome in prenatally detected CHD with and without extracardiac structural anomalies on prenatal scan are depicted in Table 3. Of the CHD cases identified on prenatal scan without any extracardiac structural anomalies (n = 384) 10.9% had an aneuploidy (of which 45.2% trisomy 21 [T21] presenting with atrioventricular septal defect, 31.0% T21 with another CHD, 4.8% T18 and 7.1% Turner syndrome). Of the CHD cases without a prenatal diagnosis (n = 1912) 11.3% (95% confidence interval [95% CI] 9.4–13.2) had an aneuploidy and 4.9% (95% CI 3.6–6.2) a genetic syndrome. In the total cohort (n = 1912) 2.0% (95% CI 1.4–2.6) had a 22q11 deletion (n = 39). Other genetic syndromes (e.g. CHARGE, Williams, Holt–Oram syndrome) were diagnosed in 3.9% (n = 75) of the total cohort.

Gestational age at referral

The mean gestational age at prenatal referral to a tertiary centre was 22+3 weeks before and 19+3 weeks after the introduction of the screening programme (difference 21 days, 95% CI 16–26, P < 0.001). Since the introduction of screening the ‘late’ referrals (after 24 weeks of gestation, the legal limit for termination of pregnancy in the Netherlands) decreased from 31.0% to 6.7% (difference 24.3%, 95% CI 19.3–29.3, P < 0.001). Seventy-three percent of the cases detected after 24 weeks of gestation since 2007 (n = 34), are CHD that are known to develop later in gestation or that are difficult to detect around 20 weeks of gestation (e.g. coarctation, pulmonary stenosis, VSD).

Mortality

The TOP rate in all severe CHD cases (including cases with chromosomal or other extracardiac anomalies), prenatally diagnosed before 24 weeks of gestation remained similar; 50.0% (124/248) before the introduction versus 52.7% (263/499) after the introduction of screening (difference 2.7%, 95% CI -4.9 to 10.3, P = 0.486). The TOP rate in isolated CHD, diagnosed before 24 weeks of gestation remained similar; 28.6% (28/98) before versus 34.7% (74/213) after the introduction of screening (difference 6.1%, 95%CI-4.9 to 17.1, P = 0.282). The first-year mortality in liveborn infants with isolated CHD decreased from 13.2% to 12.2% (difference 1.0%, 95% CI -2.7 to 3.7, P = 0.612). The presurgical mortality of liveborn infants with isolated CHD was 7.0% before versus 6.3% after the introduction of screening (difference 0.7%, 95% CI -2.0 to 3.6, P = 0.640). The first year postsurgical mortality in isolated CHD went from 6.7 to 6.3% (difference 0.4%, 95% CI -2.4 to 3.2, P = 0.801).
DISCUSSION

Main findings

This study presents more than 1900 fetuses and infants with severe CHD. The study assessed the effect of a national screening programme on the prenatal detection rate. A total birth prevalence of severe CHD of 2.7 per 1000 births was found. The prenatal detection rates of severe CHD increased significantly after the introduction of the programme to 59.7% and 44.2% for isolated severe CHD. The highest prenatal detection rates were found in hypoplastic left heart syndrome, other univentricular defects and the complex heart defects with atrial isomerism, all >93%. The groups of CHD in which the prenatal detection has remained relatively low are valve abnormalities in biventricular hearts and pulmonary or systemic venous return anomalies.

### Table 3

Aneuploidy, genetic syndromes and pregnancy outcome in prenatally detected severe CHD with and without extracardiac structural anomalies identified on prenatal scan*

<table>
<thead>
<tr>
<th>Identified on prenatal scan</th>
<th>CHD without extra structural anomalies n (%)</th>
<th>CHD with extra structural anomalies* n (%)</th>
<th>CHD with SUA, IUGR, poly-, or oligohydramnios n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated</td>
<td>303 (78.9)</td>
<td>49 (10.4) †</td>
<td>29 (65.9)</td>
<td>381 (42.3)</td>
</tr>
<tr>
<td>Aneuploidy</td>
<td>42 (10.9)</td>
<td>255 (54.0)</td>
<td>7 (15.9)</td>
<td>304 (33.8)</td>
</tr>
<tr>
<td>Genetic syndrome ‡</td>
<td>21 (5.5)</td>
<td>40 (8.5)</td>
<td>2 (4.5)</td>
<td>63 (7.0)</td>
</tr>
<tr>
<td>Extracardiac anomaly §</td>
<td>18 (4.7)</td>
<td>125 (26.5)</td>
<td>7 (15.9)</td>
<td>150 (16.7)</td>
</tr>
<tr>
<td>Missing □</td>
<td>0 (0)</td>
<td>2 (0.4)</td>
<td>0 (0)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Live birth</td>
<td>261 (68.0)</td>
<td>116 (24.6)</td>
<td>28 (63.6)</td>
<td>405 (45.0)</td>
</tr>
<tr>
<td>TOP</td>
<td>109 (28.4)</td>
<td>283 (60.0)</td>
<td>11 (25.0)</td>
<td>403 (44.8)</td>
</tr>
<tr>
<td>IUFD</td>
<td>14 (3.6)</td>
<td>73 (15.4)</td>
<td>5 (11.4)</td>
<td>92 (10.2)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>384 (42.7)</td>
<td>472 (52.4)</td>
<td>44 (4.9)</td>
<td>900 (100)</td>
</tr>
</tbody>
</table>

Legend:
- SUA; single umbilical artery
- IUGR; intra-uterine growth restriction
* Extracardiac structural anomaly on prenatal scan includes single or multiple structural anomaly/ies, fetal hydrops and nuchal translucency >3.5mm.
† In these cases on prenatal scan an extracardiac structural anomaly was identified, but after birth the infant developed normal (e.g. suspicion esophageal atresia, pyelectasis, hydrops).
‡ Genetic syndrome includes microdeletions, duplications and monogenic disorders.
§ Extracardiac anomaly after birth without chromosomal anomaly (includes single extracardiac anomaly significantly affecting postnatal outcome or multiple extracardiac anomalies).
□ Data missing on presence of extracardiac anomalies after birth
Strengths and limitations
Due to the gradual and heterogeneous introduction of prenatal screening worldwide and continuous technical developments, it has always been challenging to study the actual effects of screening programmes in pregnancy. Therefore, the relatively late, but uniform introduction of a national screening programme in the Netherlands offered a unique possibility to study the effect of such an instrument. This study represents the largest cohort of severe CHD in an unselected population with such a detailed analysis per cardiac diagnosis since the 1990s. The total birth prevalence that was found in this study is consistent with a worldwide accepted birth prevalence of severe CHD. Pathology databases, sudden infant death records and emergency ward admissions were studied for potential cases and we assume that we did not miss a significant number of them. The lost-to-follow-up rate in our cohort is very low. Maximum efforts were made to identify possible risk factors, but maternal data were not available in all postnatally diagnosed cases. However, it is well known that 90% of CHD occur in populations without any identifiable risk factor, so we assume that the effect of potential confounders will be very limited. We could not obtain data of cases that were screened as negative in the study region, but that were born and diagnosed with CHD outside the study region. Those data, however, would not influence the detection rates of our screening programme. Furthermore, we conclude from the data before 2007 that in a small number of pregnancies, an ultrasound was already performed around 20 weeks of gestation in the absence of a screening programme. This implies that the true effect of prenatal screening is even more significant than we can demonstrate here.

Interpretation
The detection rate after the introduction of the programme was 59.7%, which is remarkably high in an unselected population, compared with similar programmes that never exceeded 25–45%. The detection rate of isolated CHD with the screening programme is especially noteworthy (44.2%), compared with 16–23% published in other studies. The highest prenatal detection rates (>93%) were found in CHD with abnormal four-chamber view (hypoplastic left heart syndrome, other univentricular defects and the complex heart defects with atrial isomerism) and exceed previously published series. Hypoplastic right heart syndrome is more frequently overlooked (prenatal detection rate 66.7%), as it may present with a relatively good right ventricular cavity around 20 weeks of gestation. Significant improvements were made in the prenatal detection of several (ductal dependent) outflow tract and aortic arch anomalies that require examination of the outlet views in addition to the four-chamber view. The prenatal detection of valve abnormalities in biventricular hearts and pulmonary or...
systemic venous return anomalies has remained relatively low. Valve abnormalities can be very subtle in the first half of pregnancy and usually need the use of colour Doppler. Doppler was not compulsory in the Dutch screening programme. Furthermore, obstructive lesions can develop or progress as pregnancy advances and may not be recognisable around 20 weeks of gestation.\(^\text{32,33}\) We believe that another factor that adds to the persistent low detection rates is the fact that training programmes do not sufficiently teach how to diagnose those anomalies in four-chamber and sagittal views. The difficulty in the diagnosis of anomalies of the aortic arch has been widely acknowledged,\(^\text{34}\) yet this study showed a significant increase in the detection rate of coarctation of the aorta. The high detection rates in this study are in our opinion, explained by the thoroughly organised national screening programme with well-defined ultrasound protocols. Uniform training,\(^\text{35}\) and quality assessments of the ultrasonographers, warrant a quality level that is not restricted to urban areas only, as this cohort contains large rural areas as well.\(^\text{29,36}\) A standardised educational programme for ultrasonographers, comparable to the one in the Netherlands, was described by Levy et al.\(^\text{7}\) They reached a prenatal detection rate of 74.1% within an integrated managed care consortium. Their study cohort was, however, rather small.

Several studies have shown that the prenatal identification of specific types of CHD reduces mortality.\(^\text{15–19,37}\) In this study, the first-year mortality, as well as the presurgical mortality in liveborn infants with isolated severe CHD, remained similar. Mortality in the first year is influenced by multiple factors and perioperative care improves, so it is difficult to show a significant effect of prenatal screening. The detection rate of (ductal dependent) outflow tract anomalies hopefully will improve because of the increased awareness of the importance of the three-vessel view and its inclusion in the Dutch screening protocol as a compulsory item from 2012.\(^\text{26,38}\) It is plausible that mortality will consequently decrease.

**Conclusion**

We have shown that a thoroughly organised national screening programme has resulted in a significant increase in prenatal detection of severe CHD up to 59.7% in an unselected population. More than 90% of the prenatal diagnoses were made before 24 weeks of gestation. Prenatal detection of CHD remains challenging, especially for ultrasonographers who are minimally exposed to these anomalies. We are convinced that continued improvement of training programmes can contribute to even higher prenatal detection.
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LETTER TO THE EDITOR

Dear Sir,

We have read with interest the article by van Velzen and co-workers that reports a significant increase in prenatal detection rate of congenital heart disease (CHD) after the introduction of a national screening programme in the Netherlands. Recently we analysed the prenatal detection rate of 1865 fetuses with a morphological CHD, diagnosed in pregnancy till their 1st year of age, in the province of Antwerp, Belgium, using data from the European Surveillance of Congenital Anomalies-Antwerp (EUROCAT) over 16 years. Antwerp represents almost 30% of all births in Flanders (the northern part of Belgium).

In contrast to van Velzen et al. our data revealed a disappointingly low prenatal detection rate of 29.3% for all morphological CHD and 40.2% for severe CHD. Only 48.0% of these were diagnosed before the end of the 24th week of pregnancy. This was 51.0% for severe CHD. Therefore the detection rate of morphological CHD before the end of the 24th week is 14.1% and 20.5% for severe CHD. The increasing trend of the detection rate over this 16-year period is significant (**p** < 0.0001) (table 1). Probably this is the effect of the mandatory ultrasound course during the training for obstetrics.

Both our group and the one from van Velzen have similar demographic characteristics; Flanders and the Netherlands constitute geographic neighbours.

In Flanders, standard midtrimester anomaly scans are being performed for over 18 years already. Local guidelines are based on the guidelines of the International Society of Ultrasound. The last 10 years, the Flemish Association of Gynaecology and Obstetrics (VVOG) in collaboration with the Flemish Society of Ultrasound (VVVE) have made major efforts, to offer training to all sonographers. In contrast to the Netherlands, no licence is required to perform the anomaly scan and reimbursement by national health insurance is independent from training and qualification.

The improving detection rate in the group of van Velzen is clearly the result of better ultrasound screening. The study shows that training followed by certification and permanent quality control are mandatory to maintain the level, which may be expected by women.

Our numbers confirm that constant training can significantly improve detection percentage of CDH in a general population.

Sincerely,

Dr. Paul Ramaekers, Dr. Dominique Mannaerts, Prof. Dr. Yves Jacquemyn
REFERENCES


REPLY

Sir,

We thank colleagues Ramaekers, Mannaerts, and Jacquemyn for their positive comments on our article. They report a markedly lower detection rate for severe congenital heart disease (CHD) in a comparable population, despite efforts to adequately train all ultrasonographers.

They state that certification and permanent quality control may be an important determinant in our detection rates. Although the aim of the study was not to compare the monitoring system in the Netherlands with other systems, we do agree that quality control may contribute to our good results. In the Netherlands, prenatal screening is centrally organised, with a uniform protocol and regulations. The quality control is divided in eight prenatal screening regions, affiliated with the eight academic fetal medicine units and clinical genetics departments. These eight regions are responsible for and carry out quality monitoring of prenatal screening. In this system, licensing is compulsory. In order to perform anomaly scans, an ultrasonographer requires a license from one of the acknowledged training institutes, as well as a contract with one of the eight prenatal screening regions. Without these prerequisites, insurance companies will not reimburse. National regulations on quality management of the anomaly scan comprise a minimal number of anomaly scans per year (250 per year for starters, and 150 per year for experienced ultrasonographers) and a biannual review of their anomaly scans: the regional quality manager checks images of five randomly selected anomaly scans and scores these scans according to a nationally developed scoring system. We believe that these measures help to maintain the high quality of the anomaly scans. The cost-effectiveness of this quality monitoring system has not been investigated. The cost of a routine anomaly scan in the Netherlands is €160, of which €17 is used to run the regional centres. The overhead costs of the National Health Service (RIVM) must also be taken into account. On the other hand, missed congenital defects would also introduce costs to society. These types of costs are extremely difficult to compare. We agree with Ramaekers et al. that if prenatal screening is offered to women, then quality monitoring should be mandatory, and we strongly believe that the Dutch quality monitoring system contributed to our CHD detection rates. We did not, however, elaborate on these details extensively in our article, as the system itself was not our topic of study. The comment from Ramaekers et al. provides us with a welcome opportunity to explain more about this important underlying aspect of our study.