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Prenatal detection of aortic coarctation in a well-organized screening setting: Are we there yet?

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Abstract

Objective: We aimed to assess current prenatal detection rate (DR) of aortic coarctation (CoA) and its impact on neonatal outcome in the Netherlands to evaluate the efficacy of the Dutch screening protocol in which the cardiac four-chamber view, outflow tracts and three-vessel view are compulsory.

Methods: All prenatally and postnatally diagnosed CoA cases between 2012 and 2021 were extracted from our PRECOR-registry. Annual DRs were calculated with a focus on the trend over time and attributing factors for detection. Postnatal outcome was compared between prenatally detected and undetected cases.

Results: 49/116 cases (42.2%) were detected prenatally. A higher chance of detection was found for cases with extracardiac malformations (71.4%; $p = 0.001$) and the more severe cases with an aortic arch hypoplasia and/or ventricular septal defect (63.2%; $p = 0.001$). Time-trend analysis showed no improvement in DR over time ($p = 0.33$). Undetected cases presented with acute circulatory shock in 20.9% and were more likely to have severe lactic acidosis ($p = 0.02$) and impaired cardiac function ($p < 0.001$) before surgery.

Conclusion: Even in a well-organized screening program, the DR of CoA still requires improvement, especially in isolated cases. The increased risk of severe lactic acidosis in undetected cases stresses the need for urgent additions to the current screening program, such as implementation of the three-vessel trachea view and measurement of outflow tracts.

Key points

What's already known about this topic?

- Aortic coarctation is known for low prenatal detection rates in prenatal screening programs.
- A prenatal diagnosis decreases the chance of severe neonatal morbidity or death.

It has been presented orally at the AEPC 2022.

What does this study add?

- Even in a well-organized screening setting with regular quality monitoring, prenatal detection of aortic coarctation is still low, especially for isolated cases.
- The addition of the three-vessel trachea view and the measurement of the outflow tracts to a prenatal screening program are highly recommended.

1 | INTRODUCTION

The implementation of the second-trimester anomaly scan has led to a significant improvement in the detection of congenital heart defects (CHDs).[1,2] Prenatal detection of aortic coarctation (CoA), however, remains challenging. The majority of papers report detection rates below 35%, although large variations can be found depending on the level of organization of the screening system.[1,3–5] Ventricular and semilunar valve-size disproportion with a smaller left side are the main predictors in the fetal screening setting, but these findings can be subtle or even absent at 20 weeks GA, resulting in a moderate to low sensitivity of screening programs.[6–8] Many other ultrasonographic markers have been reported over the past decades in order to improve the detection rates.[9–13] Despite the quantity of literature on this topic, CoA is still one of the most frequently missed diagnoses.[14]

CoA can be life-threatening in severe cases, requiring urgent postnatal care to ensure survival. Prenatal detection is therefore critically important as timely management with prostaglandins after birth can prevent acute circulatory shock and metabolic acidosis and thus significantly reduces neonatal morbidity and mortality.[15]

In the Netherlands, the fetal anomaly screening program is centrally organized with strict regulations regarding training, certification, and regular quality monitoring of the ultrasonographers. Given the high detection rates for severe CHDs in general (82.4% for transposition of the great arteries, 59.6% for all CHDs combined including smaller defects such as ventricular septal defects), the quality of the Dutch prenatal screening program is considered high.[1,16] The latest reported prenatal detection rate of CoA in the Netherlands was published shortly after the introduction of the second-trimester anomaly scan, indicating a disappointing detection rate of only 25.7% (study period 2007–2012).[1] At that time, only the cardiac four-chamber view and left and right outflow tracts were mandatory. Since 2012, the three-vessel view was added to the national screening program and remained the only scan plane for the great vessels in the mediastinum. We hypothesized that continuous training of the sonographers and expansion of the scan protocol with the three-vessel view as a mandatory plane should have increased the detection rate of CoA. Knowledge of the current prenatal detection rate is crucial to evaluate the efficacy of our screening protocol. Therefore, the main objective of this study was to explore the prenatal detection of CoA, with a focus on the trend over time and the impact on neonatal outcome, by assessing results from both pre- and postnatally diagnosed cases.

2 | METHODS

2.1 | Dutch prenatal screening program

The prenatal screening program in the Netherlands is coordinated on a national level. The majority (95%) of the second-trimester anomaly scans are performed in primary healthcare centers, as only pregnancies with an increased risk of fetal congenital malformations are scanned in tertiary care centers for prenatal diagnosis. All ultrasonographers performing the second-trimester anomaly scan have received training in a systematic and similar manner and execute a uniform protocol. Their quality is regularly monitored by regional surveillance committees through a biannual image analysis program and the obligation to perform a minimum of 150 anomaly scans per year. Passing these monitoring measures is compulsory for an ultrasonographer to maintain his/her license to perform anomaly scans.[17] The Dutch fetal anomaly scan is mainly conducted between 18 and 21 weeks and comprises the following mandatory cardiac planes: the four-chamber view, the left and the right outflow tract, and since 2012, the three-vessel view.[18] Other routine obstetric scans require solely the cardiac four-chamber view and are mainly performed by physicians qualified in routine measurements only (e.g., fetal growth and fetal well-being). Once a congenital (heart) defect is suspected, the woman is referred to a tertiary care center for an extensive fetal echocardiography.

2.2 | Standard postnatal management

All cases with a prenatal suspicion for CoA or aortic arch hypoplasia (AAH) in the Netherlands are delivered in a tertiary care center for maternal-fetal medicine with expertise on CHDs, enabling the required obstetric and neonatal care. When born, the neonates are admitted to the neonatal intensive care unit (NICU) for observation. If the clinical prenatal suspicion for CoA or AAH is high, prostaglandin therapy is started directly after birth, while neonates with low suspicion are initially admitted without prostaglandins. During admission, the neonates are continuously monitored with frequent (a minimum of once daily) collection of arterial blood gases and lactate levels. Echocardiography is performed daily during this period. When a truly ductal-dependent aortic coarctation is confirmed, surgery is usually planned approximately 5–7 days after birth, when fetal-to-neonatal transition is optimized. For cases with a postnatally diagnosed CoA or AAH, postnatal management depends on the presence

of an acute cardiovascular event. Cases who present in an acute setting are stabilized first with prostaglandins and/or inotropic support and/or mechanical ventilation, followed by surgery shortly after, while cases who present in a non-acute situation allow for planned surgery.

2.3 | Case and data collection

All cases in this retrospective cohort study were collected from the PRECOR registry, a regional registry for prenatal and postnatal diagnosed CHDs. The PRECOR registry was initiated by the two tertiary care centers in the North-West region of the Netherlands (Leiden University Medical Center and Amsterdam University Medical Center) that collaborate as one center in the care for fetuses and infants with CHDs. This collaboration is named Center for Congenital Heart Defects Amsterdam and Leiden (CAHAL) and covers approximately 40% of all live births in the Netherlands. All cases in this region with a prenatal or postnatal diagnosis of severe CHD (requiring surgery within the first year of life) have been entered into the PRECOR registry since 2002. The prevalence of severe CHDs in the registry is 2.3 per 1000 live births, which corresponds with the previously reported prevalence of severe CHD, attesting to the completeness of this registry. The data collection for the PRECOR registry has previously been described more extensively.[1] The two centers collaborating in the CAHAL have a general privacy statement informing patients that their data can be used for retrospective scientific research. The Medical Ethics Review Committee Leiden-Den Haag-Delft reviewed the study protocol (G21.170) and granted a waiver of consent due to the retrospective character of the study.

Cases fulfilling the following inclusion criteria were extracted from the PRECOR registry: a prenatal or postnatal diagnosis of CoA or AAH, born between 2012 and 2021, where aortic arch surgery (coarctectomy with end-to-end anastomosis or aortic arch repair) was required within the first year of life, or, in case of termination of the pregnancy or intrauterine fetal demise, where the diagnosis was confirmed by post-mortem examination or post-mortem magnetic resonance imaging (MRI). We only included cases with CoA or AAH as the single major cardiac anomaly with or without anomalies in other organ systems. Cases with additional small cardiac defects were included (venous aberrations (persistent left superior vena cava [PLSVC] or interrupted inferior vena cava without left isomerism), bicuspid aortic valve, restrictive foramen ovale and ventricular or atrial septal defect). Of the cases with a small left heart or borderline left ventricle, only those without structural malformations of left-sided heart structures other than CoA/AAH (such as aortic valve stenosis, mitral valve dysplasia or stenosis) were included. We cross-checked the case list with our surgical lists and the neonatal mortality registries to check for missing cases. Of note, in this study, we did not review post-mortem databases of the departments of pathology to identify cases in which death had occurred outside the hospital as the travel distances to a nearby hospital are small in the Netherlands and therefore out-of-hospital deaths are rare. More importantly, in a previous study at the start of the PRECOR registry (at that time 1912 cases with CHD), we did include a search of the port-mortem national database for cardiac defects and only identified one missed case with transposition of the great arteries, which underlines again the completeness of the registry.[1]

Data on the cardiac diagnosis, the presence of an extracardiac congenital malformation or genetic disorder, and postnatal outcome were retrieved from the PRECOR registry and electronic patient records. The postnatal echocardiography, surgical report, autopsy report or post-mortem MRI report defined the final diagnosis used for analysis. In other words, the cases with CoA were those who required coarctectomy with end-to-end anastomosis or showed a short narrowing at autopsy report/post-mortem MRI, while the AAH cases were those who required aortic arch repair for a longer segment with the use of cardiopulmonary bypass or showed a complete hypoplastic arch at autopsy report/post-mortem MRI. Ventricle septal defects (VSDs) were only reported in this study if surgical closure was required. For neonatal outcome analysis, we differentiated between true "simple" CoA cases (referring to those where CoA was the single cardiac anomaly with the exception of atrial septal defect, restrictive foramen ovale, bicuspid aortic valve or venous aberrations) and cases comprising AAH and/or VSD, as it can be expected that the latter have a higher chance of prenatal detection, and a different neonatal outcome due to the need for sternotomy and cardiopulmonary bypass. Also cases with extracardiac malformations were differentiated from cases without extracardiac malformations. Concerning neonatal outcome parameters, severe lactic acidosis was defined as lactate plasma levels >5 mmol/L.

2.4 | Statistical analysis

Descriptive statistics were used to analyze the study population: continuous variables with normal distribution were shown as mean (±SD, standard deviation), continuous variables with skewed distribution as median (interquartile range [IQR]) and categorical variables as frequencies (percentage). All variables were compared between the detected and undetected groups. The independent samples *t*-test or the Mann-Whitney U test was performed to compare continuous data. For categorical variables, we performed a chi-square test or, if the expected number was <5, a Fisher's exact test. The chi-square trend analysis was used to study changes in the detection rate over time. A *p*-value of <0.05 was considered statistically significant. All statistics were performed with SPSS Statistics 25.0 (IBM Corp., Armonk, New York, USA).

3 | RESULTS

A total of 116 cases were eligible for inclusion in this study. All inclusions comprised live-born cases, as all cases ending with a termination of pregnancy or intrauterine fetal demise did not consent to

post-mortem autopsy or MRI to confirm the diagnosis. At baseline, the two groups (detected vs. undetected) did not differ significantly in relevant parameters. Although the undetected group comprised significantly more male fetuses, gender was not considered to affect our results (Table 1).

3.1 | Prenatal detection

The overall prenatal detection rate for CoA and AAH was 42.2% (49/116), with a significantly higher chance of detection for cases comprising an AAH and/or VSD compared to cases with a simple CoA (63.2% vs. 32.1%; $p = 0.001$). The presence of extracardiac structural malformations also significantly increased the chance of prenatal detection, as the detection rate for simple CoA cases with extracardiac malformations was 71.4%, while the detection rate for simple CoA cases without extracardiac malformations was 23.4% ($p = 0.001$) (Table 2). The presence of PLSVC did not differ between detected and undetected cases (8.2% vs. 4.5%) and therefore did not affect the detection rate ($p = 0.45$). Moreover, time-trend analysis showed no significant improvement in the detection rate over time ($p = 0.33$) (Figure 1). The median gestational age (GA) at

TABLE 1 Baseline characteristics for 116 pregnancies, according to prenatal detection

	Prenatal detection		
	Yes ($n = 49$)	No ($n = 67$)	p-value
GA at prenatal detection, weeks	20.9 (20.0–24.4)	n/a	
Detected >24 weeks	12 (24.5)	n/a	
Postnatal age at detection, days	n/a	11.0 (7.0–41.3)	
Male, gender	25 (51.0)	51 (76.1)	0.005
GA at birth, weeks	38.9 (38.0–40.0)	39.4 (38.0–40.3)	ns
Preterm delivery[a]	7 (14.3)	6/53 (11.32)	ns
Cesarean section	9 (18.4)	5/32 (15.6)	ns
Birthweight, grams	3197 ± 681	3336 ± 580	ns
<2500 g	6 (12.2)	6/62 (9.7)	ns

Note: Data given as mean ± SD, median (IQR) or *n* (%).

Abbreviations: GA, gestational age; IQR, interquartile range; n/a, not applicable; ns, not significant.

[a]<37 weeks GA.

TABLE 2 Prenatal detection rate with its attributing factors

	Prenatal detection			
	Yes (%) $n = 49$	No (%) $n = 67$	OR (95% CI)	p-value
Total cases	49 (42.2)	67 (57.8)		
Simple aortic coarctation[a]	25 (32.1)	53 (67.9)		
Without extracardiac anomaly[b,c]	15 (23.4)	49 (76.6)	0.1 (0.03–0.45)	0.001
Without genetic abnormality[d]	21 (29.2)	51 (70.8)	0.2 (0.11–0.52)	0.080
Aortic arch hypoplasia and/or VSD	24 (63.2)	14 (36.8)	3.6 (1.61–8.20)	0.001
Aortic arch hypoplasia	16 (64.0)	9 (36.0)	3.13 (1.24–7.87)	0.013
VSD	19 (65.5)	10 (34.5)	3.61 (1.49–8.77)	0.003

Note: Data are given as *n* (%).

Abbreviations: OR, odds ratio; VSD, ventricular septal defect.

[a]Defined as cases with CoA as a solitary cardiac finding with the exception of atrial septal defect, restrictive foramen ovale, bicuspid aortic valve, venous aberrations.

[b]Defined as all malformations that should be visible on the standard fetal anomaly scan.

[c]Additional findings were: unilateral clubfoot, hydronephrosis, unilateral pelvic kidney, increased nuchal translucency, horseshoe kidney, single umbilical artery, hydrocephalus, intrauterine growth restriction, echogenic bowel.

[d]Only pathogenic and likely pathogenic variants were included. Genetic findings were: Turner syndrome, Kabuki syndrome, Trisomy 21, Jacobsen syndrome, 22q11 deletion, ATR-16 syndrome and Neurofibromatosis.

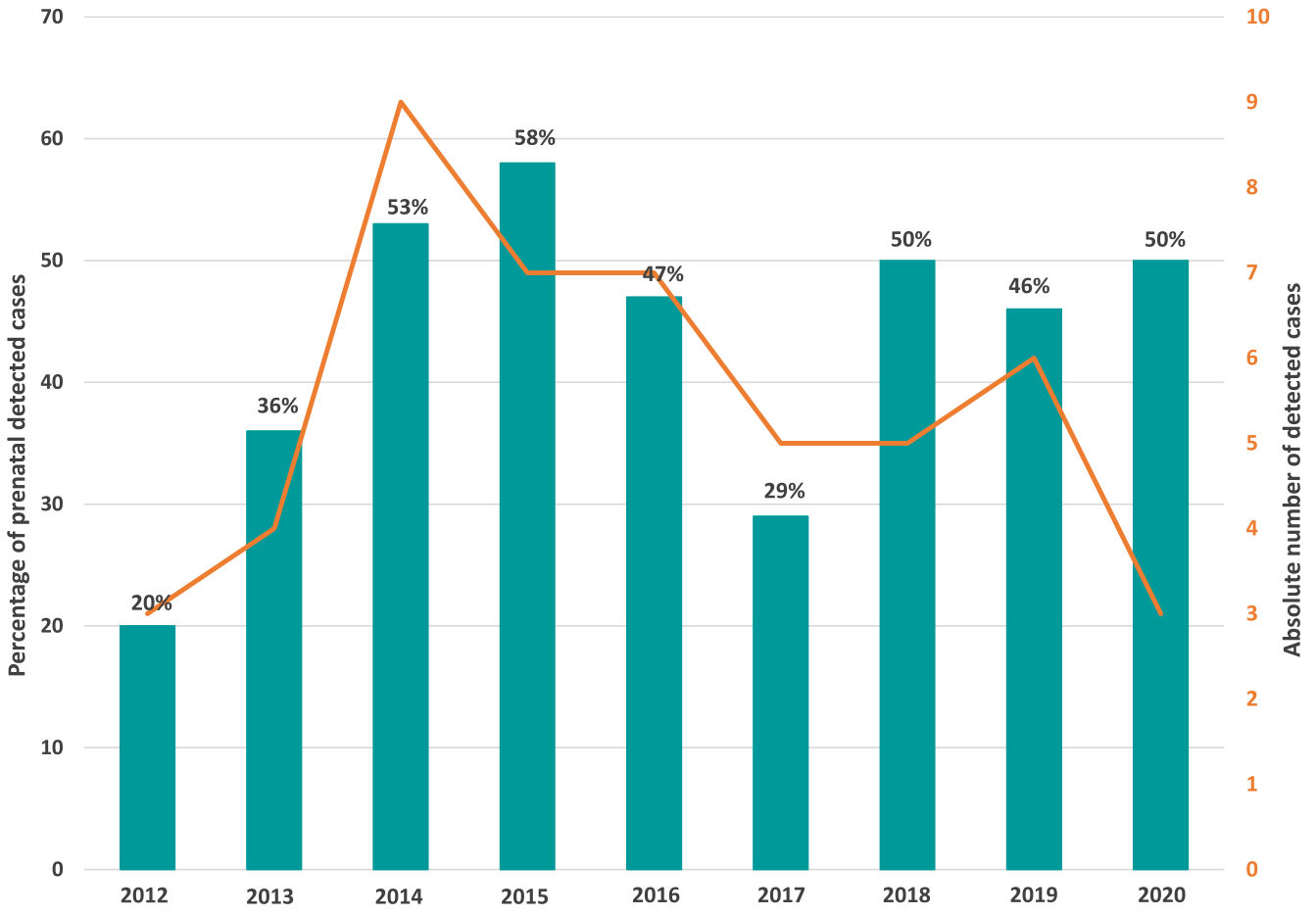

FIGURE 1 Yearly trends in prenatal diagnosis of aortic coarctation. [Colour figure can be viewed at wileyonlinelibrary.com]

detection was 20.9 weeks (IQR 20.0–24.4). The most common indications for referral for extensive fetal echocardiography were signs of CoA (such as ventricular and semilunar valve-size disproportion; 71.4%), followed by an increased nuchal translucency in the first trimester (14.3%), suspicion of a VSD (6.1%), extracardiac structural malformation(s) (6.1%) and an irregular fetal heart rhythm (2.1%).

3.2 | Neonatal outcome

Neonatal outcome is depicted in Table 3, in which we present simple CoA cases and cases comprising an AAH and/or VSD separately, as the latter require a more extensive surgical procedure, including the use of a sternotomy and cardiopulmonary bypass, which may negatively affect neonatal outcome. In total, 14 undetected cases (20.9%) presented with acute circulatory shock, of which 13 were simple CoA cases. Consequently, undetected simple CoA cases had a higher incidence of severe lactic acidosis compared to the prenatally detected simple CoA cases (8.7% vs. 34.9%; $p = 0.02$). Of note, the severe lactic acidosis in the two prenatally diagnosed cases was caused by respiratory insufficiency due to pulmonary hypertension. Additionally, undetected simple CoA cases more frequently required inotropic support for hemodynamic stabilization (50.9% vs. 8.0%; $p < 0.001$) and a longer mechanical ventilation time (1.2 vs. 0.1 days, $p = 0.01$) during the preoperative period, while prenatally detected simple CoA cases had a longer NICU stay (12.0 vs. 7.0 days, $p = 0.01$), which predominantly consisted of days prior to surgery (7.5 vs. 2.6 days; $p = 0.001$). After surgery, the length of NICU stay did not differ between the two groups (4.5 vs. 4.4 days; $p = 0.95$). Cases comprising AAH and/or VSD showed no significant differences in NICU admission and duration of mechanical ventilation between the detected and undetected groups. Three cases with extensive AAH and VSD died in the postoperative period. All were known prenatally. Two cases had to be resuscitated after acute circulatory failure. In one of them, ECMO support was initiated but irreversible severe neurological damage prevented ECMO weaning. In the third patient, Kabuki syndrome was present and an acute increase in pulmonary hypertension resulted in multi-organ failure.

4 | DISCUSSION

This study in an unselected population demonstrates that even in a well-organized screening setting, the prenatal detection rate for CoA still requires improvement, as in 57.8% of the cases, the heart defect

TABLE 3 Neonatal outcome of cases according to prenatal detection status, differentiated between simple CoA cases and cases comprising AAH and/or VSD

Simple CoA cases	Prenatal detection		*p*-value (95% CI)	OR (95% CI)
	Yes (n = 25)	No (n = 53)		
Hospital stay				
Duration NICU admission, days[a]	12.0 ± 12.0	7.0 ± 5.1	0.012 (1.13 to 8.79)	
Prior to surgery, days[a]	7.5 ± 8.5	2.6 ± 3.5	0.001 (2.18 to 7.58)	
Number of admissions <1 year	1.7 ± 0.6	1.3 ± 0.6	0.019 (0.06 to 0.62)	
Of which NICU	1.2 ± 0.4	1.1 ± 0.3	0.043 (0.01 to 0.32)	
Duration mechanical ventilation				
Preoperative, days	0.1 ± 0.4	1.2 ± 2.1	0.011 (−1.92 to −0.26)	
Postoperative, days	2.8 ± 5.1	2.2 ± 1.1	0.555 (−1.50 to 2.72)	
Total days <1 year	2.0 (1.0–2.0)	3.0 (2.0–5.0)	0.017	
Lowest plasma pH level[b]	7.29 (7.02–7.41)[d]	7.18 (6.60–7.42)[d]	0.014 (0.22 to −0.19)	
pH < 7.2	2/23 (8.7)	16/46 (34.8)	0.020	0.2 (0.04–0.86)
Highest plasma lactate level, mmol/L[b]	3.3 (0.5–6.8)[d]	5.7 (0.8–18.0)[d]	0.048 (−4.80 to −0.03)	
Lactate >5 mmol/L	4/20 (20.0)	15/43 (34.9)	0.231	0.5 (0.13–1.65)
Inotropic support[c]	2/25 (8.0)	27/53 (50.9)	<0.001	0.1 (0.01–0.39)
Mortality <1 year	0 (0.0)	0 (0.0)	n/a	
Cases with AAH and/or VSD	**Prenatal detection**		***p*-value (95% CI)**	**OR (95% CI)**
	Yes (n = 24)	**No (n = 14)**		
Hospital stay				
Duration NICU admission, days[a]	20.3 ± 15.5	13.5 ± 10.7	0.122 (−1.91 to 15.41)	
Prior to surgery, days[a]	11.9 ± 14.9	5.4 ± 5.2	0.063 (−0.36 to 13.26)	
Number of admissions <1 year	2.3 ± 1.0	1.9 ± 0.8	0.228 (−0.24 to 0.97)	
Of which NICU	1.6 ± 0.6	1.5 ± 0.7	0.696 (−0.35 to 0.52)	
Duration mechanical ventilation				
Preoperative, days	2.3 ± 3.3	1.6 ± 3.0	0.565 (−1.52 to 2.74)	
Postoperative, days	5.6 ± 3.7	4.1 ± 2.9	0.192 (−0.76 to 3.64)	
Total days <1 year	7.5 (5.0–12.0)	6.0 (3.5–10.0)	0.301	
Lowest plasma pH level[b]	7.26 (7.02–7.38)[d]	7.25 (6.80–7.41)[d]	0.736 (−0.07 to 0.10)	
pH < 7.2	2/24 (8.3)	2/13 (15.4)	0.602	0.5 (0.06–4.03)
Highest plasma lactate level, mmol/L[b]	3.6 (1.1–6.9)[d]	4.3 (1.4–16.6)[d]	0.478 (−2.44 to 1.17)	
Lactate >5 mmol/L	2/24 (8.3)	3/13 (23.1)	0.321	0.3 (0.04–2.22)
Inotropic support[c]	8/24 (33.3)	4/14 (28.6)	1.000	1.3 (0.30–5.26)
Mortality <1 year	3/24 (12.5)	0 (0.0)	0.283	1.1 (0.98–1.33)

Note: Data given as mean ± SD, median (IQR) or n (%) unless specified.

Abbreviations: AAH, aortic arch hypoplasia; IQR, interquartile range; NICU, neonatal intensive care unit; OR, odds ratio; VSD, ventricular septal defect.

[a]At admission of aortic arch surgery.

[b]Determined from arterial blood gas analysis (not umbilical cord artery) prior to aortic arch surgery.

[c]Prior to aortic arch surgery.

[d]Data given as mean (range).

was not detected before birth. The prenatal detection rate of simple CoA cases without extracardiac malformations was even lower with only 23.4% of the cases detected prenatally. The importance of a prenatal diagnosis is illustrated by the fact that in prenatally undetected cases, 20.9% of the neonates were admitted with acute circulatory shock and consequently had a significantly higher incidence of severe lactic acidosis and impaired cardiac function requiring inotropic support before surgery.

4.1 | Prenatal detection

The quality of the Dutch prenatal screening program is considered one of the highest worldwide, which is reflected in the previously reported detection rate of 82% for transposition of the great arteries.[16] Also the presented detection rate of 42.2% for neonatal CoA in this study is from a global perspective quite good. Previous cohort studies reporting the detection rate of CoA show large differences between countries and even between geographical areas within a country, varying between 0% in Malta and 66% in France.[1,3,5,19] These differences depend largely on the expertise of the screening center, the selection of the study population (hospital vs. population-based) and difference in screening protocols (e.g., France includes a routine third trimester scan). Of note, in contrast to our study, previous studies assessed a more heterogeneous CoA group without specifically describing the detection rate of purely isolated CoA cases. We demonstrated that a considerable number of cases present with additional extracardiac malformations (12.1%) or had an AAH and/or VSD (36.1%), which significantly increased the probability of prenatal detection (23.4% for simple CoA cases without extracardiac malformations vs. 71.4% for simple CoA cases with extracardiac malformations and 63.2% for AAH and/or VSD cases). Therefore, the detection of isolated simple CoA cases requires the largest improvement.

It is well known that isolated outflow tract lesions are the most challenging to detect in a routine screening setting, in particular those with a normal four-chamber view or subtle signs, such as left-right asymmetry. In the Netherlands, the three-vessel view is currently the only mandatory scanning plane for the great vessels in the upper mediastinum. Compared to before the implementation of this plane in 2012, the presented detection rate for CoA is a substantial improvement (25.7% vs. 42.2%, $p = 0.023$).[1] Time-trend analysis in this study could, however, not identify a significant improvement in the detection rate in the years after 2012, despite continuous postgraduate training of the sonographers. This illustrates clearly that the three-vessel view is not enough for the prenatal detection of CoA. It is well established that the three-vessel-trachea view is effective in the detection of anomalies of the outflow tracts and the aortic arch, and that this plane is easy to obtain.[16,20,21] Measurements of the outflow tracts may furthermore have some values in the detection of CoA.[10] Therefore, in accordance with the ISUOG guideline, we advocate the addition of the three-vessel-trachea view and the measurement of the outflow tracts to fetal anomaly screenings protocols to increase awareness of obstructive aortic arch lesions.[22] Complete detection at time of the second-trimester anomaly scan is, however, impossible as a part of the cases shows completely normal symmetrical cardiac anatomy at that time due to disease development later in gestation or even after birth through the involvement of ductal tissue.[14,23] Therefore, postnatal screening tools such as assessment of the femoral pulse and Pulse Oximetry screening after birth are encouraged as well to expedite the diagnosis when missed prenatally.[24] Also the implementation of a standard third-trimester cardiac screening with the focus on ventricular and great arterial disproportion is an area to be explored, as left-to-right disproportion is more clear in the third trimester. The sensitivity of prenatal ultrasound in predicting aortic coarctation at this gestational age is, however, shown to be very low, and therefore, the implementation of such a standard screening would increase the false-positive rates enormously.[25] A false-positive diagnosis implies birth and neonatal care admission in a tertiary center with cardiothoracic services, leading to parental anxiety. Nonetheless, one could advocate that a high false-positive rate is acceptable if it increases the prenatal detection of CoA as well. In this context, third-trimester indicators for true CoA should be investigated properly with a focus on the balance between false positives and the false negatives.

4.2 | Neonatal outcome

The benefit of a prenatal diagnosis is emphasized by the neonatal outcome of our cases, in particular of the simple CoA cases. In total, one in five undetected cases presented in acute circulatory shock. All but one of these were simple CoA cases. As a consequence, these cases encountered a 5-fold higher odds ratio for severe lactic acidosis. This is of utmost clinical importance, as it has been shown that severe lactic acidosis is associated with an impaired neurodevelopmental outcome.[26,27] Moreover, undetected simple CoA cases required more frequently inotropic support, longer mechanical ventilation and admission time during the preoperative period, illustrating that neonates with a missed diagnosis are in a worse clinical state at presentation. The only other paper assessing the neonatal outcome of solely CoA or AAH cases is of *Franklin et al.*, which reports 32 cases in a different era (1994–1998). Franklin's study shows that a prenatal diagnosis improves pre-operative conditions and demonstrated that a prenatal diagnosis is life-saving, as three undiagnosed cases (9.4%) died at home.[15] In our study, the three neonatal deaths (2.6%) occurred in the prenatally detected group; yet their heart defect belonged to the most severe end of the spectrum. Of note, the absence of mortality in the undetected group, where a substantial part of cases presented with a life-threatening scenario, attests to the high quality of neonatal care in our region.

On the other hand, prenatally detected simple CoA cases in our study showed an increased length of NICU stay, which was completely attributable to a longer preoperative admission. The longer preoperative admission time is not surprising as it is used for observation to confirm the presence of a truly ductal-dependent

CoA, which prevents unnecessary interventions, and to optimize fetal-to-neonatal transition. Postnatally diagnosed cases either presented in an acute setting, which required surgery urgently after stabilization (usually within 2 days), or presented in non-acute situation, which allowed for planned surgery, both resulting in short preoperative admission times.

The neonatal outcome of the complex cases comprising AAH and/or VSD did not differ between the prenatally and postnatally detected groups, as they consist of a more severe subset of cardiac patients in which the effect of the heart defect by itself is much larger. Some of the morbidity/mortality could not be prevented by a prenatal diagnosis, which explains our findings. Nonetheless, we believe that a prenatal diagnosis would also be beneficial for this group as it enables proper prenatal counseling and both clinical and parental preparation for postnatal management; factors with great impact that were/could not be measured in this study. Moreover, we assessed only short-term neonatal outcome parameters, while it is likely that a missed diagnosis with a poor clinical condition at presentation has impact on long-term neurodevelopment.

4.3 | Limitations

Caution should be taken when interpreting our results due to the retrospective character of the study. In particular, maternal data could not be retrieved from all postnatally diagnosed cases. It was, however, not the objective of the study to identify maternal risk factors and it is known that the effect of maternal confounders is limited.[14] The detection rate in this cohort could be underestimated as we performed a strict selection procedure where all cases with termination of pregnancy or intrauterine fetal demise without confirmed diagnosis at post-mortem examination were excluded. From a clinical perspective, however, these cases often presented with severe additional pathology (e.g., fetal hydrops in case of Turner syndrome). Moreover, out-of-hospital deaths were not included in this study, although they are extremely rare in the Netherlands as the travel distances to a nearby hospital are small. We state that the presented detection rate is representable for the Dutch screening system, in which the three-vessel view is the only mandatory plane for the great vessels in the mediastinum. Therefore, our results should be interpreted accordingly, as they might be different in countries in which additional scanning planes are mandatory.

5 | CONCLUSION

Even in a well-organized screening program, the detection rate of CoA (42.2%) remains disappointingly low compared to other severe CHDs. This is especially so for simple CoA cases without extracardiac malformations (23.4%). The increased risk of lactic acidosis in undetected cases stresses the need for major improvement. Therefore, the implementation of the three-vessel trachea view and measurement of outflow tracts to each fetal anomaly screening protocol is important. Future studies should focus on promising techniques, such as artificial intelligence to automate imaging interpretation,[28] in an attempt to improve prenatal detection of CHD in a routine screening setting.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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