



## REGULAR ARTICLE

## Newborn pulse oximetry screening in the context of a high antenatal detection rate of critical congenital heart disease

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**Abstract****Aim:** Assess the potential additional benefit from pulse oximetry screening in the early detection of critical congenital heart disease in a country with a well-developed antenatal ultrasound screening programme.**Methods:** Live-born infants, pregnancy terminations and stillbirths from 20 weeks' gestational age, between 2013 and 2015, with critical cardiac defects defined as primary or secondary targets of pulse oximetry screening were identified. Critical defects were those resulting in the death of a fetus or an infant in the first 28 days after birth, or a defect requiring intervention in the first 28 days.**Results:** Two hundred and sixty-eight infants and Fetuses were identified. Antenatal detection rates improved from 69% to 77% over the study period. An associated comorbidity improved antenatal detection rates. Twenty-seven live-born infants were diagnosed after discharge: 15 aortic arch obstruction (AAO); 10 d-loop transposition of the great arteries (d-TGA), and two total anomalous pulmonary venous drainage (TAPVD). Of these, five with AAO, nine with d-TGA and likely both with TAPVD could potentially have been detected with oximetry screening.**Conclusion:** The antenatal detection of critical cardiac anomalies continues to improve in New Zealand. Despite high antenatal detection rates for most lesions, universal postnatal oximetry screening has the potential to improve early detection.**KEYWORDS**

congenital heart disease, screening strategies, newborn

**1 | INTRODUCTION**Congenital heart disease (CHD) is the most common group of congenital malformations and the leading cause of infant mortality from birth defects.<sup>1</sup> Most cardiac anomalies are amenable to surgery, butdelayed diagnosis is a barrier to the timely initiation of potentially life-preserving interventions.<sup>2</sup> In the past, two screening strategies have been used to detect cardiac disease prior to the onset of symptoms and thereby reduce the risk of acute cardiovascular collapse: (a) antenatal ultrasound and (b) newborn physical examination.**Abbreviations:** AAO, Aortic arch obstruction; AS, Aortic stenosis; CHD, Congenital heart disease; CoA, Coarctation of the aorta; CYMRC, Child and Youth Mortality Review Committee; DORV, Double outlet right ventricle; d-TGA, d-loop Transposition of the great arteries; HLHS, hypoplastic left heart syndrome; IAA, Interrupted aortic arch; PA, Pulmonary atresia; PMMRC, Perinatal and Maternal Mortality Review Committee; PS, Pulmonary stenosis; TA, Tricuspid atresia; TAPVD, Total anomalous pulmonary venous drainage; ToF, Tetralogy of Fallot.

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Routine ultrasound examination of the fetal heart was introduced in the 1980s.<sup>3</sup> Despite advances in this field, the sensitivity of this tool to detect cardiac anomalies remains modest in many maternity settings.<sup>4-6</sup> Similarly, the effectiveness of the newborn physical examination is limited as most infants with CHD are asymptomatic at birth. Several studies have reported that newborn physical examination fails to detect more than 50% of infants with critical cardiac disease.<sup>7,8</sup>

Critical cardiac anomalies may not produce visible cyanosis, but a degree of hypoxaemia will be present in the majority of these infants. This has led to the utilisation of pulse oximetry as a screening tool to identify underlying cardiac disease in newborn infants, and in the last decade, pulse oximetry screening has become an established practice in many parts of the world.<sup>9</sup> Some have, however, cited high antenatal detection rates as the reason for not considering the introduction of pulse oximetry screening.<sup>10</sup>

In order to assess the remaining deficiencies in the detection of critical CHD and the likely impact of pulse oximetry screening in New Zealand, a country with a well-developed antenatal ultrasound screening programme, we reviewed the timing of diagnosis and outcomes in a population-based cohort of fetuses and newborns with critical CHD in a period prior to the widespread use of pulse oximetry screening. Pulse oximetry screening was introduced at several hospitals and primary maternity units in New Zealand in 2016. The country has a population of 4.9 million, of which approximately 50% live in urban areas with tertiary medical facilities.

## 2 | METHODS

This was a retrospective review of live-born infants as well as pregnancy terminations, and stillbirths from 20 weeks' gestational age with critical cardiac defects identified as primary or secondary targets of pulse oximetry screening.<sup>11</sup> Primary targets were those anomalies commonly associated with hypoxaemia, namely: d-loop transposition of the great arteries (d-TGA) with and without ventricular septal defect(s); hypoplastic left heart syndrome (HLHS); pulmonary atresia (PA); tetralogy of Fallot (ToF); total anomalous pulmonary venous drainage (TAPVD); tricuspid atresia (TA) and truncus arteriosus. Secondary targets may also produce low oxygen saturation levels and were as follows: coarctation of the aorta (CoA); interrupted aortic arch (IAA); double outlet right ventricle (DORV); Ebstein's anomaly; aortic stenosis (AS) and pulmonary stenosis (PS). CoA and IAA were combined into a single category named aortic arch obstruction (AAO), and AS and PS were collectively referred to as valvular stenosis.

Associated major extra-cardiac or chromosomal anomalies were described as co-morbidities and were included in the analyses. Critical defects were defined as those resulting in the death of a fetus or an infant in the first 28 days after birth, or a defect requiring cardiac catheter or surgical intervention in the first 28 days after birth. Pregnancy terminations were included. In New Zealand, pregnancy terminations can be done beyond 20 weeks' gestational age if

### Key notes

- Critical cardiac defects are a heterogeneous group of anomalies that present diagnostic challenges.
- The timely detection of critical cardiac defects enables early intervention, which offers the best chance of survival.
- The yield from postnatal oximetry screening will depend in part on the number of cases missed on antenatal ultrasound screening.

there are significant concerns about the mother's mental or physical health. Under these circumstances, there is no limit to the gestation at which a pregnancy can be terminated.

To better understand factors affecting antenatal diagnosis, defects were grouped together based on the imaging required to identify the anomaly on a fetal anatomy ultrasound scan. There were three groups: Group A = anomalies visible on a four-chamber view; Group B = anomalies requiring visualisation of the outflow tracts and Group C = arch view, three-vessel view (3VV) and three-vessel trachea view (3VT) or other views required to identify the anomaly (Table 1).

This study focused on the 3 years (2013-2015) prior to the introduction of pulse oximetry when antenatal ultrasound and newborn physical examination were the only screening tools utilised to identify CHD in this population. Data were obtained from the National Paediatric Cardiology and Cardiac Surgical databases and supplemented with information extracted from the following New Zealand Ministry of Health data collections: (a) the National Maternity Collection which contains national statistical, demographic and clinical data on maternity services from up to 9 months before and three months after a birth; (b) the Perinatal and Maternal Mortality Review Committee (PMMRC) and (c) the Child and Youth Mortality Review Committee (CYMRC). Fetal, neonatal and infant deaths are reported to these committees. In the event of an unexplained death, coronial jurisdiction is taken, which generally results in a post-mortem examination that is performed by a perinatal pathologist.

### 2.1 | Statistical analysis

Median and range were used to describe continuous variables, and percentages were used for categorical variables. The chi square test was used for comparisons between categorical variables. All *P* values are two tailed, and a value <.05 was considered statistically significant.

### 2.2 | Ethics approval

This study was approved by the Health and Disability Ethics Committees of New Zealand (MEC/12/EXP/077/AM02).

**TABLE 1** Incidence and antenatal detection rates

	All live births, stillbirths & pregnancy terminations n = 178 889			Live births	Stillbirths	Pregnancy terminations
	Total n	Incidence n per 1000	Antenatal diagnosis n (%)	Total n (%)	Total n (%)	Total n (%)
Primary targets	178	1.0	141 (79)	123 (69)	12 (7)	43 (24)
Secondary targets	90	0.5	54 (60)	71 (79)	5 (6)	14 (15)
Group A (4 chamber view)						
HLHS	38	0.21	37 (97)	17 (45)	4 (10)	17 (45)
Pulmonary atresia	24	0.13	21 (88)	14 (58)	3 (13)	7 (29)
Tricuspid atresia	7	0.04	7 (100)	3 (43)	2 (28)	2 (28)
Ebstein's anomaly	3	0.02	3 (100)	1 (33)	-	2 (67)
Total Group A	72		68 (94)	35 (49)	9 (12)	28 (39)
Group B (Outflow tract view)						
Tetralogy of Fallot	26	0.15	25 (96)	11 (42)	2 (8)	13 (50)
Truncus arteriosus	6	0.03	6 (100)	4 (67)	-	2 (33)
DORV	21	0.12	20 (95)	13 (62)	4 (19)	4 (19)
Valvular stenosis	16	0.09	8 (50)	13 (81)	1 (6)	2 (13)
Total Group B	69		59 (86)	41 (60)	7 (10)	21 (30)
Group C (Arch view/3VV/3VT/Other)						
d-TGA	70	0.39	43 (61)	67 (96)	1 (1)	2 (3)
AAO	50	0.28	23 (46)	44 (88)	-	6
TAPVD	7	0.04	2 (29)	7 (100)	-	-
Total Group C	127		68 (54)	118 (93)	1 (1)	8 (6)
All	268	1.5	195 (73)	194 (72)	17 (7)	57 (21)

Note: P value: Antenatal detection rate (comparison group A, B & C) <.001.

Abbreviation: 3 VV, 3 vessel view; 3VT, 3 vessel and trachea view; AAO, aortic arch obstruction; DORV, Double outlet right ventricle; d-TGA, d-loop transposition of the great arteries; HLHS, hypoplastic left heart syndrome; TAPVD, total anomalous pulmonary venous drainage.

### 3 | RESULTS

Over the 3 years from 2013 to 2015, there were 178 889 live births, stillbirths and pregnancy terminations beyond 20 weeks' gestation in New Zealand. There were 178 infants with a cardiac defect identified as a primary target and a further 90 with a secondary target anomaly. Of these, 72 were in Group A, 69 in Group B and 127 in Group C. The highest incidence was recorded for d-TGA (0.39 per 1000) followed by AAO (0.28 per 1000) and HLHS (0.21 per 1000) (Table 1). There were 57 (21%) pregnancy terminations and 17 (6%) stillbirths, 18 (24%) of which had an associated major extra-cardiac or chromosomal anomaly. One hundred and ninety-four (73%) infants were born alive; the median gestation at birth was 38 weeks (range 25-42 weeks) and the median birth weight was 3232 g (range 750-4710 g). Eighteen (9%) infants were born at a gestational age <37 weeks. Of the 18 (9%) with a birth weight less than 2500 g, 11 (61%) had a gestational age of ≥37 weeks. Co-morbidities were present in 42 (22%) live-born infants.

An antenatal detection rate of >85% was achieved for all but four anomalies: TAPVD (29%); AAO (46%); valvular stenosis (50%) and d-TGA (61%). There was an improvement over time in the rate of antenatal detection from 69% in 2013 to 77% in 2015. Overall 195 (73%)

were diagnosed in the antenatal period, a further 44 (16%) were detected in the postnatal period prior to discharge, 27 (10%) received a diagnosis after discharge from the place of birth and 2 (1%) stillborn fetuses were diagnosed on post-mortem examination. The antenatal detection rate was significantly higher for anomalies visible on a four-chamber view of the fetal heart;  $P = .001$  (Table 1). Of those diagnosed after discharge, 15 (52%) had AAO, 10 (35%) d-TGA, and 2 (7%) TAPVD. Despite improvement in the antenatal detection of AAO and d-TGA, rates for these lesions remained modest (Tables 2 and 3). Based on the estimated sensitivity of pulse oximetry for specific anomalies,<sup>12</sup> an additional nine infants with d-TGA, five with AAO and two with TAPVD could potentially have been detected with this screening test prior to discharge (Table 3). The presence of an extra-cardiac or chromosomal anomaly significantly increased the likelihood of antenatal detection with 54 of 60 (90%) diagnosed before birth compared with 141 of 208 (68%,  $P < .001$ ) with isolated heart disease.

Thirty-five (18%) live-born infants died in the first year. There were 14 (8%) deaths among 173 that were operated on. All 21 of those that did not undergo a cardiac intervention died (Table 4). Mortality was significantly higher in the presence of a co-morbidity (45% vs 10%;  $P < .001$ ). A higher mortality rate was observed among

**TABLE 2** Antenatal detection rates by year

	2013	2014	2015
<b>Antenatal detection rate, n/total (%)</b>			
Cardiac anomalies			
HLHS	11/12 (92)	10/10 (100)	16/16 (100)
Pulmonary atresia	10/10 (100)	6/8 (75)	6/10 (100)
Tricuspid atresia	3/3 (100)	3/3 (100)	1/1 (100)
Ebstein's anomaly	1/1 (100)	1/1 (100)	1/1 (100)
Tetralogy of Fallot	7/8 (88)	10/10 (100)	8/8 (100)
Truncus arteriosus	3/3 (100)	1/1 (100)	2/2 (100)
DORV	5/5 (100)	5/5 (100)	10/11 (91)
Valvular stenosis	4/4 (100)	3/8 (38)	1/4 (25)
d-TGA	12/25 (48)	16/23 (70)	15/22 (68)
AAO	7/20 (35)	6/11 (55)	10/19 (53)
TAPVD	1/2 (50)	0/4 (0)	1/1 (100)
Total	64/93 (69)	61/84 (73)	70/91 (77)

Abbreviations: AAO, aortic arch obstruction; DORV, double outlet right ventricle; d-TGA, d-loop transposition of the great arteries; HLHS, hypoplastic left heart syndrome; TAPVD, total anomalous pulmonary venous drainage.

those diagnosed in the antenatal period compared with a postnatal diagnosis;  $P < .001$ . The four live-born infants who died following a postnatal diagnosis all had isolated cardiac anomalies. One infant with d-TGA was diagnosed on post-mortem examination after he collapsed and died at home on day 11 after birth. The other three infants (two with d-TGA and one with aortic valve stenosis) became symptomatic shortly after birth and died prior to reaching the cardiac intervention centre. The 1-year mortality rate ranged from 7% for Group C to 46% for Group A;  $P < .001$ . Low birth weight resulted in a higher mortality rate as did birth before 37 weeks' gestation (Table 4).

## 4 | DISCUSSION

This population-based study demonstrated that New Zealand has excellent antenatal detection rates for the majority of anomalies defined as pulse oximetry screening targets and that these rates have improved over time. Exceptions apply to those anomalies that require more specialised ultrasound views and techniques to enable an antenatal diagnosis—the highest number of missed cases was recorded for d-TGA and AAO. The ability to detect CoA on antenatal ultrasound is further limited by the fact that coarctation may only occur after the arterial duct closes. As a result, the indicators of coarctation have limited predictive value before birth. In the absence

of an extra-cardiac co-morbidity that may raise the suspicion of an associated cardiac defect, it is particularly challenging to detect these anomalies in the antenatal period.

The antenatal detection achieved in this study is superior to rates reported by many other developed countries.<sup>4,6,13</sup> This may be attributed to various factors. First, the definition of critical CHD varies among studies; and therefore, an exact comparison cannot be made. Furthermore, New Zealand is able to report on whole-population data due to the availability of fetal and infant data sources. Other jurisdictions may not be able to include antenatal diagnoses that resulted in pregnancy terminations and stillbirths. In the last decade, there have been significant efforts in New Zealand to improve the antenatal detection of congenital anomalies. For CHD, this included sonographer training and the addition of the 3VV, 3VT and sagittal arch views to enhance the quality of mid-trimester fetal anatomy scans. These views require a greater degree of skill and are not always obtainable. Nevertheless, their use has increased the likelihood of detecting d-TGA in particular.<sup>2</sup> The positive impact of training programmes on the success of antenatal cardiac screening has been widely acknowledged and there has been a general trend of increasing antenatal detection rates in well-organised health systems.<sup>14,15</sup>

The relationship between timing of diagnosis and survival is well recognised in the population of infants with congenital cardiac anomalies.<sup>16,17</sup> The effect of New Zealand's efforts to improve outcomes for those with cardiac anomalies through early detection is evident in this study. We previously reviewed infants with major CHD born in New Zealand between 2006 and 2010 and reported an antenatal detection rate of 46% for those with critical anomalies. The estimation was made that four babies die each year in New Zealand as a result of late-diagnosed critical CHD.<sup>18</sup> Although only live-born infants were included in that study, a comparison can be drawn with those born alive during the 2013-2015 study period during which only four deaths occurred among infants diagnosed after birth. Three infants died despite being diagnosed prior to discharge from hospital. A post-mortem diagnosis of d-TGA was made on the fourth infant who died at home at 9 days of age.

Not only was there an improvement in the overall antenatal detection rate between this study period and the 2006-2010 period, but also within the 2013-2015 period. Antenatal ultrasound and newborn physical examination combined detected 89% of the 2013-2015 cohort. The improvement observed over time can largely be attributed to better antenatal detection of d-TGA and AAO. However, the timely detection of these anomalies as well as valvular stenosis and TAPVD remains a challenge and is substantially less than for other critical cardiac defects. The high incidence of d-TGA and AAO and the number of cases missed on prenatal screening mean that these anomalies are a key target of early postnatal detection in jurisdictions such as this with a high antenatal detection for most other critical anomalies.

Transposition of the great arteries can result in significant hypoxaemia; consequently, the sensitivity of pulse oximetry for the detection of this condition is high.<sup>12,19</sup> The opposite is true for AAO for

**TABLE 3** Potential impact of combined screening strategies for anomalies with antenatal detection rate <85%

	Live born	Antenatal diagnosis	Pre-discharge diagnosis	Missed diagnoses	Sensitivity: pulse oximetry <sup>a</sup>	Potential additional pre-discharge diagnoses with pulse oximetry	Detection with combined strategies
d-TGA	67	40 (60)	17 (25)	10 (15)	92%	9	66 (98)
AAO	44	17 (39)	12 (27)	15 (34)	36%	5	34 (77)
TAPVD	7	2 (29)	3 (43)	2 (28)	91%	2	7 (100)
Valvular stenosis	13	5 (38)	8 (62)	-	-	-	13 (100)

Abbreviations: AAO, aortic arch obstruction; d-TGA, d-loop transposition of the great arteries; TAPVD, total anomalous pulmonary venous drainage.

<sup>a</sup>Prudhoe et al<sup>12</sup>. - anomaly specific sensitivity derived from 13 studies involving 258 809 participants.

**TABLE 4** One-year mortality among live-born infants

	N	Mortality, n (%)	P value
	194	35 (18)	
Co-morbidity			
Yes	42	19 (45)	<.001
No	152	16 (10)	
Prematurity (<37 wk)			
Yes	18	6 (33)	NS
No	157	29 (18)	
Low birth weight (<2500 g)			
Yes	18	6 (33)	NS
No	157	29 (18)	
Type of defect			
Group A	35	16 (46)	<.001
Group B	41	11 (27)	
Group C	118	8 (7)	
Timing of diagnosis			
Antenatal	123	31 (25)	<.001
Postnatal	71	4 (6)	
Cardiac intervention			
Yes	173	14 (8)	NE
No	21	21 (100)	

which the sensitivity ranges between 20% and 40%.<sup>20-22</sup> Therefore, the maximal benefit of newborn pulse oximetry screening will likely be to those with d-TGA.

In New Zealand, the newborn physical examination is undertaken by the lead maternity carer, who most commonly is a midwife. This examination includes auscultation of the heart, palpation of femoral pulses and an assessment of colour and perfusion. The recommendation is that this examination should be completed within 48 hours after birth, but is often performed within the first hours as it is common for women and infants to be discharged home or to a primary maternity unit within 4-6 hours after the birth. The impact of improved awareness of clinical staff postnatally has been highlighted. A Swedish study reported that 68 of a cohort of 86 (79%) prenatally undiagnosed infants with d-TGA were detected on routine clinical examination or because signs, and symptoms were present prior to routine postnatal investigations. Seven (8%) were diagnosed as a result of pulse oximetry screening. Infants born at hospitals where pulse oximetry screening was routinely performed were diagnosed earlier than those born at hospitals that were not offering screening. The difference remained significant after excluding those detected by pulse oximetry.<sup>19</sup>

Congenital cardiac disease is a heterogeneous group of anomalies. Limitations persist in terms of what can be offered to some of these infants. The severity of the disease or associated anomalies will often dictate the outcome regardless of an early diagnosis. Indeed, in this study a significantly higher mortality rate was observed among those diagnosed in the antenatal period. This relates

to the relative simplicity of diagnosing single ventricle anomalies, that are associated with a guarded outlook, such as HLHS and TA by means of the four-chamber view of the fetal heart. The presence of an extra-cardiac or chromosomal anomaly also improves the likelihood of antenatal detection significantly,<sup>4,13</sup> but the presence of these co-morbidities is another poor prognostic indicator. A higher mortality rate was observed among those born before 37 weeks' gestation. The negative impact on prognosis when cardiac disease occurs in association with prematurity has been recognised.<sup>23,24</sup>

The severity of a cardiac anomaly and the presence of an associated co-morbidity have also been identified as factors associated with pregnancy termination and stillbirth rates.<sup>5,25</sup> In this study, the highest proportion of fetal deaths was recorded for Ebstein's anomaly (67%), followed by ToF (58%), TA (57%) and HLHS (55%). In addition, maternal factors and gestational age at the time of diagnosis have been shown to impact on the decision to terminate a pregnancy.<sup>5,25</sup> Dependent on jurisdiction, there may be legal barriers to termination of a pregnancy, especially at an advanced gestation.

In this setting with a well-developed antenatal screening programme, the anomalies that continue to pose diagnostic challenges in the fetus are also those known to have excellent post-intervention survival.<sup>26,27</sup> There should be ongoing efforts to improve antenatal detection of CHD. This strategy in combination with postnatal pulse oximetry screening and clinical vigilance can provide these infants with the best chance of an early postnatal diagnosis that will enable life-saving interventions. The importance of the timing of diagnosis for infants with d-TGA in particular has been highlighted. For some, a balloon atrial septostomy may be urgently required to achieve haemodynamic stability. Failure to reach a centre capable of performing this intervention may result in death.<sup>2</sup>

The value of pulse oximetry screening for the detection of other hypoxaemic conditions such as respiratory or infectious diseases has been recognised<sup>28,29</sup> and may be of particular importance in settings where the majority of those with cardiac disease are diagnosed in the antenatal period. In view of this, we designed an intervention study to explore the impact of pulse oximetry screening in our population. This study demonstrated that newborn infants with cardiac and other hypoxaemic conditions can benefit from pulse oximetry screening. These findings are described elsewhere.<sup>30</sup>

It is a limitation of this study that data for fetal loss prior to 20 weeks' gestation are not available. However, the timing of the fetal anatomy scan in New Zealand dictates that very few women carrying a fetus with a cardiac anomaly will be seen by specialist services prior to 20 weeks' gestation to discuss management options.

## 5 | CONCLUSION

Efforts to improve the quality of antenatal ultrasound screening in New Zealand have resulted in a higher proportion of CHD being diagnosed before birth. In combination with newborn physical examination, 89% currently receive a diagnosis prior to discharge. However, in this setting with a well-developed antenatal screening

programme, there are groups of patients that remain at risk either as a result of disease severity, associated co-morbidities or missed diagnoses. Pulse oximetry screening could aid in the early detection of those missed by other screening strategies, but is not without limitations. A combined approach, with antenatal ultrasound screening, postnatal oximetry screening, a high index of suspicion and a health-care system geared to rapid response when CHD does present, is likely to provide the best outcome for infants with critical cardiac anomalies.

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## CONFLICT OF INTEREST

There are no conflicts of interest or financial relationships relevant to this article to disclose.

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