Antenatal Detection of Treatable Critical Congenital Heart Disease Is Associated with Lower Morbidity and Mortality

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Objective To establish the impact that timing of diagnosis and place of birth have on neonatal outcomes in those with readily treatable critical congenital heart disease.

Study design This was a population-based study with a complete national cohort of live-born infants with transposition of the great arteries and aortic arch obstruction in New Zealand between 2006 and 2014. Timing of diagnosis, place of birth, survival to surgery, in-hospital events, and neonatal mortality were reviewed. Live births with a gestation of ≥35 weeks and without associated major extracardiac anomalies were included for analysis.

Results A total of 166 live-born infants with transposition of the great arteries and 87 with aortic arch obstruction were included. Antenatal detection increased from 32% in the first 3 years to 47% in the last 3 years ($P = .05$). During the same period, neonatal mortality decreased from 9% to 1% ($P = .02$). No deaths occurred after surgical intervention. An antenatal diagnosis was associated with decreased mortality (1/97 [1%] vs 11/156 [7%]; $P = .03$) and birth outside the surgical center was associated with increased risk of mortality (11/147 [7%] vs 1/106 [1%]; $P = .02$). Those with an antenatal diagnosis required fewer hours of mechanical ventilation ($P = .02$) and had shorter durations of hospital stay ($P = .05$) compared with those diagnosed >48 hours after birth.

Conclusions The mortality risk for transposition of the great arteries and critical aortic arch obstruction is greatest before cardiac surgery. Improved antenatal detection allowing delivery at a surgical center is associated with reduced mortality. *(J Pediatr 2019;204:66-70).*

Congenital heart disease is a common birth defect with a reported prevalence ranging between 4 and 12 per 1000 live-born infants.[1] The spectrum of anomalies ranges from those with minimal or no clinical significance to complex lesions such as those with single-ventricle anatomy where either the pulmonary or systemic circulation cannot be supported independently. The term critical has been used to define severe forms of cardiac disease, often described as those that require intervention or result in death within the first month after birth.[2]

Aortic arch obstruction (AAO), such as coarctation of the aorta and interrupted aortic arch, as well as d-loop transposition of the great arteries (d-TGA), are predominantly duct-dependent critical anomalies that result in acute cardiorespiratory compromise and death if not recognized and treated early. Excellent outcomes are possible after cardiac surgery for both of these conditions. For example, the 20-year survival after an arterial switch operation for d-TGA is >95%[3] and long-term follow-up studies after aortic coarctation repair report survival beyond 65 years of age.[4,5]

Determining the preoperative mortality risk for these anomalies and its relationship to the timing of diagnosis and resource use can inform planning of healthcare strategies to minimize risk. New Zealand is a country with a publicly funded healthcare system and a single pediatric cardiac surgical center. This population-based study was designed to test the hypothesis that there is a relationship between the timing of diagnosis, place of birth, and neonatal outcomes for infants born with d-TGA and critical AAO.

Methods

We identified all infants with d-TGA and critical AAO born in New Zealand between 2006 and 2014. Critical AAO included coarctation of the aorta and interrupted aortic arch that resulted in death or required intervention in the first 28 days after birth. Data were obtained from the National Paediatric Cardiology and Cardiac Surgical databases and supplemented with information extracted from the

AAO	Aortic arch obstruction
d-TGA	d-loop transposition of the great arteries
IVS	Intact ventricular septum
VSD	Ventricular septal defect

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Supported by awards from the Health Research Council of New Zealand, Starship Foundation, Middlemore Foundation, Green Lane Research and Education Fund, A + Trust Research Fund, and the New Zealand branch of the Cardiac Society of Australia and New Zealand. E.C. receives support in the form of a scholarship from Gravida National Centre for Growth and Development. The authors declare no conflicts of interest.

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https://doi.org10.1016/j.jpeds.2018.08.056

Table I. Cases excluded

	Pregnancy terminations	Still births	Live birth with comorbidities*	Antenatal detection, n (%)
n	8	5	32	—
AAO, n = 24	1	2	21	12 (50)
d-TGA, n = 21	7	3	11	15 (71)

*Comorbidities are birth at <35 weeks of gestation and/or a chromosomal or major noncardiac anomaly.

following New Zealand Ministry of Health data collections: (1) the National Maternity Collection, which contains national statistical, demographic, and clinical maternity data from up to 9 months before and 3 months after a birth; (2) the National Minimum Dataset, a national collection of all hospital discharge information, including day stay; (3) and the New Zealand Perinatal and Maternal Mortality Review Committee, containing data on all maternal and perinatal deaths in New Zealand. There is a statutory requirement that all fetal and infant deaths from 20 weeks of gestation to 28 days postnatal age be reported to this committee. Data from each dataset were combined using the New Zealand National Health Index number as a unique identifier.

For comparison, the 9-year period was divided into 3-year epochs and the timing of the diagnosis was classified as antenatal, early postnatal, or late postnatal. All antenatally diagnosed patients were born at the cardiac intervention center unless delivery occurred prematurely and before transfer could be arranged. An early postnatal diagnosis was one that was made in time for the infant to reach the cardiac intervention center within 48 hours from birth or, in the case of infants who died before arrival at the surgical center, when the diagnosis was made at their local hospital within 48 hours of birth. All postmortem diagnoses were classified as 'late postnatal'. A 48-hour cutoff was selected for the following reasons: (1) the national recommendation is that the newborn physical examination should be performed within 48 hours from birth[6] and (2) ductal constriction or closure will often occur within this time period. Survival to cardiac surgery, hours of mechanical ventilation, duration of hospital stay, and 28-day mortality were recorded for the selected cohort. Those diagnosed on postmortem examination were excluded from the analysis of in-patient events. Further exclusions to outcome analyses applied to pregnancy terminations, stillbirths, those born at <35 weeks of gestation, and infants with an associated syndrome or major noncardiac anomaly (**Table I**). Prematurity and other comorbidities were considered confounding factors that may impact on the measured outcomes.

Statistical Analyses

Categorical variables are summarized as percentages and compared with the χ^2 test or Fisher exact test. Continuous variables are presented as median, range, and IQR, and compared with the Mann-Whitney *U* test. All *P* values are 2 tailed and a value of <.05 was considered statistically significant.

Results

During the study period, there was a total of 561 226 live births, stillbirths, and pregnancy terminations (from 20 weeks of gestation) in New Zealand. There were 187 live births, stillbirths, and pregnancy terminations at >20 weeks of gestation with d-TGA and 112 with AAO, giving a population incidence of 0.33 and 0.20 per 1000 respectively. Of the 253 infants who met the inclusion criteria, 79 were born during the 3 years between 2006 and 2008, 86 between 2009 and 2011, and 88 between 2012 and 2014. The groups had similar characteristics and a male predominance was observed throughout (**Table II**). The overall male to female ratio was 2:1. Infants with d-TGA made up the majority of the cohort (166 [66%]). An associated ventricular septal defect (VSD) requiring surgical closure was present in 50 of the 166 patients with d-TGA (30%) and 40 of 87 (46%) with AAO.

Over the 9-year period, the antenatal detection rate was significantly higher for d-TGA (75/166 [45%]) compared with AAO (22/87 [25%]; *P* = .002). Improvement was also seen over the 3 epochs in the antenatal detection rate of d-TGA (*P* = .04; **Table III**), but not for AAO. This resulted in an overall improvement in antenatal detection from 32% in the first epoch to 47% in the last epoch (*P* = .05). The proportion of infants with d-TGA identified in the early postnatal period decreased over the course of the study. Therefore, there was no significant decrease in the number of infants receiving a late postnatal diagnosis.

The presence of a VSD in association with d-TGA or AAO resulted in an improvement in the likelihood of prenatal detection (42/90 [47%]) compared with anomalies with an intact ventricular septum (IVS) (55/163 [34%]; *P* = .04). This finding was most pronounced for the cohort with AAO, where 16 of 40 patients with a VSD (40%) were detected in the antenatal period compared with 6 of 47 of those with an IVS (13%; *P* = .004).

A balloon atrial septostomy was performed on 53 of the 75 (71%) with an antenatal diagnosis of d-TGA, 38 of 51 (75%)

Table II. Patient characteristics

	2006-2008	2009-2011	2012-2014
n	79	86	88
Gestational age, wk	39 (35-42)	39 (35-42)	39 (35-42)
BW, g	3390 (2030-4470)	3465 (2315-4630)	3400 (1840-4970)
Sex			
Male	50 (63)	63 (73)	61 (69)
Female	29 (37)	23 (27)	27 (31)
Type of anomaly			
d-TGA	53 (67)	56 (65)	57 (65)
IVS	41	41	34
VSD	12	15	23
AAO	26 (33)	30 (35)	31 (35)
IVS	14	16	17
VSD	12	14	14

BW, birth weight.
Values are median (range) or n (%).

Table III. Timing of diagnosis and mortality by year group and type of anomaly

	2006-2008			2009-2011			2012-2014		
	d-TGA	AAO	Total	d-TGA	AAO	Total	d-TGA	AAO	Total
n	53	26	79	56	30	86	57	31	88
Timing of diagnosis									
Antenatal	18 (34)	7 (27)	25 (32)	24 (43)	7 (23)	31 (36)	33 (58)	8 (26)	41 (47)
Early postnatal	19 (36)	-	19 (24)	19 (34)	1 (4)	20 (23)	13 (23)	3 (10)	16 (18)
Late postnatal	16 (30)	19 (73)	35 (44)	13 (23)	22 (73)	35 (41)	11 (19)	20 (65)	31 (35)
28-Day mortality	4 (8)	3 (12)	7 (9)	2 (4)	2 (7)	4 (5)	1 (2)	-	1 (1)

$P = .02$ for total deaths in epoch 1 vs 3.
Values are n (%).

with an early postnatal diagnosis, and 18 of 40 (45%) with a late postnatal diagnosis.

There was a total of 12 (5%) deaths. Mortality in the first 28 days decreased across the first to last epochs from 9% between 2006 and 2008 to 1% between 2012 and 2014 ($P = .02$). The decrease in mortality over this time period was most marked for those with an AAO (from 12% to 0%; **Table III**). The median age at death was 9 days (range, 0-26 days). Two deaths occurred at the surgical center: a term infant with an antenatal diagnosis of d-TGA died as a result of birth trauma and a late-preterm low birth weight infant with d-TGA died on day 13 before undergoing definitive surgery. This infant was diagnosed early in the postnatal period and underwent balloon septostomy after transfer to the surgical center. A cause of death was not identified on the postmortem examination. There were no deaths after surgical intervention (**Table IV**).

The mortality rate among infants diagnosed after birth (11/156 [7%]) was significantly greater than for those diagnosed in the antenatal period (1/97 [1%]; $P = .03$). Importantly, mortality was associated with delivery outside the surgical center with 11 of 147 deaths (7%) in those born outside the surgical center compared with 1 of 106 inborn infants (1%; $P = .02$). Although an early postnatal diagnosis did not result in a lower mortality rate in comparison with late postnatal detection, the pattern was different for d-TGA compared with AAO. Of the deaths that occurred outside the surgical center in those with d-TGA, 4 of 5 had an early postnatal diagnosis, all had an IVS, and birth occurred a median distance of 645 km (range, 160-645 km) from the surgical center. For the AAO group, 4 of 5 had a late postnatal diagnosis and birth occurred a median of 125 km (range, 20-645 km) from the surgical center (**Table IV**).

Overall, 242 infants (96%) survived to undergo definitive repair. Those diagnosed in the antenatal period spent a median time (preoperative and postoperative) of 66 hours ventilated (IQR, 44-90 hours) compared with 83 hours (IQR, 49-130 hours) for those who received a late postnatal diagnosis ($P = .02$). This difference coincided with a shorter pre- and postoperative duration of hospital stay (17 days [IQR, 15-25 days] vs 21 days [IQR, 15-30 days]; $P = .05$).

Discussion

The findings of this study emphasize the importance of a timely diagnosis and early intervention for infants with critical AAO and d-TGA. Specifically, there was a decrease in 28-day mortality over time that coincided with an increase in antenatal detection. However, mortality in the postnatally diagnosed cases also decreased from 7 of 54 in the first period to 1 of 47 in the last period. All deaths occurred before surgical correction, highlighting not only the excellent outcome in those treated early, but also how vulnerable infants with these conditions are before surgery and how this vulnerability is magnified when recognition of serious heart disease is delayed. Infants with d-TGA born outside the immediate vicinity of the

Table IV. Summary of deaths

Years	Diagnosis	Timing of diagnosis	Birth distance from surgical center (km)	Death at surgical center	Age at death (d)
2006	AAO	Late	125	No	16
2007	d-TGA IVS	Early	160	No	0
2007	d-TGA IVS	Late*	645	No	1
2007	AAO	Late*	645	No	1
2007	AAO	Late	20	No	9
2007	d-TGA IVS	Early	645	No	0
2008	d-TGA IVS	Early	645	Yes	13
2009	AAO	Late*	20	No	26
2009	d-TGA IVS	Late*	360	No	15
2009	d-TGA IVS	Antenatal	0	Yes	0
2010	AAO	Late*	360	No	11
2014	d-TGA IVS	Early	210	No	0

Total deaths after antenatal diagnosis = 1/97. Total deaths after a postnatal diagnosis = 11/156.
$P = .03$.
*Postmortem diagnosis.

surgical center are at risk of death even when diagnosed in the early postnatal period; for infants with AAO, death is largely confined to infants where the diagnosis occurs late after birth. In both cases, a coexisting VSD provided protection—either by expediting antenatal diagnosis or by decreasing the hemodynamic consequences of ductal closure.

The mortality risk of d-TGA and AAO is clearly greatest before cardiac intervention. The relationship between antenatal detection and improved outcomes has been demonstrated for both AAO[7,8] and d-TGA,[9,10] but preoperative survival differences as demonstrated in this study have seldom been investigated. Bonnet et al compared preoperative and postoperative outcomes for infants with an antenatal and postnatal diagnosis of d-TGA.[9] No preoperative mortality was reported in the group with an antenatal diagnosis compared with 6% in those diagnosed after birth.[9] In our study, only 1 infant with d-TGA and an associated comorbidity died after undergoing balloon atrial septostomy but before surgical intervention. Five of the 6 patients with preoperative mortality died never reaching the center where a balloon atrial septostomy could be performed. A postnatal diagnosis resulting in late initiation of treatment was also associated with increased morbidity and prolonged mechanical ventilation and hospital stay.

The time-related increase in antenatal detection is likely a result of changes to the midtrimester screening protocol. Midtrimester anatomy scans are available to all pregnant women in New Zealand from 18 weeks of gestation. This assessment includes a 4-chamber view of the fetal heart, outflow tracts, and 3-vessel views based on the International Society of Ultrasound in Obstetrics and Gynecology guideline.[11] The 3-vessel and trachea views, as well as the sagittal arch views, were increasingly used from 2010 onward after advocacy and training around the country. The addition of these views can enhance antenatal detection of outflow tract anomalies, but adequate visualization is variable and can be technically challenging. Although we have seen an improvement in the antenatal detection rate for d-TGA, the proportion of infants diagnosed during the latter part of this study remained at <60% and <30% of those with AAO were detected antenatally throughout the course of the study period. AAO in particular is difficult to detect at the midtrimester screening ultrasound examination, especially when there is no VSD, because abnormalities such as ventricular disproportion, isthmus hypoplasia, and flow abnormalities are often subtle. The reported sensitivity for the antenatal detection of aortic arch anomalies ranges from <10% to 30%.[12-14]

Many infants with critical cardiac defects remain undiagnosed before birth. In contrast with the improvement in antenatal diagnosis over time, a shift in the proportion of postnatal diagnoses that are made early after birth was not observed. The reason for this finding is likely multifactorial. In many Western countries, there has been a significant decrease in the duration of stay after an uncomplicated vaginal birth.[15,16] Physical signs and symptoms of cardiac disease are often absent in the first few hours after birth when the ductus arteriosus is patent.[17-20] A Swedish study reported that the proportion of late-diagnosed infants with critical cardiac defects increased over time, which coincided with an increased rate of discharges at <72 hours of age over the same period.[20] Infants with duct-dependent systemic circulation (coarctation in particular) were most likely to receive a late diagnosis. Abu-Harb et al reported that only 31% of infants with a left outflow tract obstruction have an abnormal newborn examination.[19] In the New Zealand maternity setting, the newborn physical examination is undertaken by the lead maternity care provider, who most commonly is a midwife. This examination includes auscultation of the heart, palpation of femoral pulses, and an assessment of color and perfusion. The recommendation is that this examination should be completed within 48 hours after birth,[6] but is often performed within the first few hours to facilitate early discharge or transfer, thus occurring at a time when the arterial duct is likely to be widely patent.

During the study period, pulse oximetry screening was not routinely undertaken in New Zealand. An early screening strategy has since been adopted by hospitals and primary birthing units participating in a feasibility study.[21] We hypothesize that several infants could have benefitted from pulse oximetry screening. The sensitivity of pulse oximetry screening for the detection of d-TGA is encouraging.[22] Consideration should, however, be given to the limitations of reliance on pulse oximetry screening in this particular group of anomalies. In this study, several infants with d-TGA and an IVS died despite an early postnatal diagnosis. All these infants were born outside the metropolitan area where the surgical center is based. Infants with d-TGA and an IVS with a restrictive foramen ovale may not respond to prostaglandin, and a balloon atrial septostomy is critical for their survival. The place of birth and distance needed to travel for balloon septostomy and expert cardiac intensive care is, therefore, a critical factor determining the outcome of these infants.

In contrast, the poor sensitivity of pulse oximetry screening for the detection of AAO remains the greatest limitation of screening for this group. Sensitivities in the range between 20% and 40% have been reported for the detection of these anomalies with pulse oximetry.[12,23,24] A relationship between the perfusion index and left ventricular output has been demonstrated[25]; therefore, the addition of this measurement may improve postnatal detection rates of AAO. The perfusion index is derived from a pulse oximeter and represents the relative amount of arterial perfusion in the examined area.[26] Its addition to pulse oximetry has been reported to increase the detection rate for cases with left heart obstruction.[27,28] Thus, pulse oximetry screening needs to be combined with strategies to increase both antenatal and postnatal detection rates.

The decrease in mortality demonstrated over the time frame of this study is perhaps greater than that anticipated by the relatively small increase in antenatal diagnosis. It is likely that other factors have contributed, including an increased awareness of congenital heart disease in the postnatal primary and secondary care setting, awareness of the importance of urgent transfer once a diagnosis is made, and improvements in intensive care management before and during transfer. ■

We thank the New Zealand Ministry of Health and the Perinatal and Maternal Mortality Review Committee for the use of their data.

Submitted for publication Jun 6, 2018; last revision received Aug 6, 2018; accepted Aug 22, 2018

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