TRANSPORT OF INFANTS WITH CONGENITAL HEART DISEASE: BENEFITS OF ANTENATAL DIAGNOSIS

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Abstract

Infants with significant congenital heart disease (CHD) typically require transport from their birth centre to a regional paediatric cardiac centre. Antenatal diagnosis of CHD allows early pre-emptive stabilization, and is associated with improved early clinical status. However, the effect of antenatal diagnosis on the transport characteristics of infants with CHD has not been previously investigated. The aim of this study was to compare the transport characteristics of infants with antenatal and postnatal diagnosis of CHD. A retrospective cohort study of all infants ≤10 days and ≥34 weeks gestation with CHD admitted to the Royal Children's Hospital, Melbourne (RCH) over 5 years. Demographic, diagnosis, and transport data were recorded. Cases of complex CHD were included in this study. Of 320 infants with complex CHD, 198 (62%) had antenatal diagnosis (ANdx), and 122 (38%) had postnatal diagnosis (PNdx). There was no significant difference in sex, birth weight or gestation between ANdx and PNdx groups. Average age of referral was 15 vs. 53.4 hrs in ANdx vs. PNdx groups. Aggregate transfer distance in the ANdx group was 2216 km and in the PNdx group was 10274km P<0.0001. 39% of infants in the PNdx group required highest acuity "Time Critical" transports, compared to 6% of ANdx infants, P=0.0001. Conversely only 11% of infants in the PNdx group had lowest acuity "non-urgent" transfers, compared to 24% of ANdx infants, P= 0.003. PNdx was associated with significantly higher rates of invasive ventilation (36% vs 20%, P=0.01) and higher rates of inotrope use (19% vs. 9%, P=0.007) during transport. *Conclusions:* Improved antenatal detection would allow for safer, less resource intense transfers of infants with CHD.

Abbreviations

ANDx- Antenatally Diagnosed

CHD- Congenital Heart Disease

CoA- Coarctation of aorta

CPAP- Continuous Positive Airway Pressure

HLHS- Hypoplastic Left Heart Syndrome

IMV- Invasive Mandatory Ventilation

iNO-Inhaled Nitric Oxide

IUGR- Intrauterine Growth Retardation

NETS- Newborn Emergency Transport Service, Victoria

PGE_1- Prostaglandin E1

PNDx- Postnatally Diagnosed

PA- Pulmonary atresia

RCH- Royal Children Hospital, Melbourne

TGA- transposition of the great arteries

Introduction

Congenital heart disease (CHD) is the most common birth defect, occurring in eight of every 1000 live births, accounting for approximately one quarter of birth defects and remains the most important cause of death in the first year of life (4,10,12).

Antenatal diagnosis of CHD has increased following the widespread introduction of routine fetal ultrasound screening, however a large proportion of infants with severe congenital heart disease remain undiagnosed until after birth. A Victorian study has previously reported an antenatal detection rate of 26.8% with trend analysis demonstrating an increase in the antenatal detection rate over the study period (2).

Antenatal diagnosis (ANdx) allows delivery to be planned, involving an experienced perinatal team who may institute early pre-emptive stabilisation. In contrast, infants with CHD who are diagnosed postnatally (PNdx), are at risk of severe deterioration and collapse before the diagnosis of CHD is suspected. Accordingly, ANdx of CHD is associated with improved physiological status, and reduced illness severity in the pre-operative period (7,11).

In seeking to investigate the potential benefits of antenatal diagnosis, an area that has been relatively overlooked is the transport of infants with CHD. Antenatally diagnosed infants may be born at or close to a paediatric cardiac centre and require either no transfer or a very short transfer of a relatively stable infant after birth. Conversely, postnatally diagnosed infants may be clinically unstable and require prolonged transfer to reach a paediatric cardiac centre, where diagnosis can be confirmed and ongoing intensive care therapy provided.

This study sought to investigate the transport implications of timing of diagnosis (ANdx vs. PNdx), on patient characteristics, cardiac therapies required during transport and resource demands.

Aim

To compare the transport and patient characteristics of newborn infants with antenatally and postnatally diagnosed congenital heart disease requiring transfer to a regional paediatric centre.

Methods

A retrospective cohort study of all infants ≤10 days old and ≥34 weeks, diagnosed with complex congenital heart disease, admitted to the Royal Children's Hospital, Melbourne (RCH) over a 5 year period (1st May 2007– 31st May 2011) was performed. RCH is the regional paediatric cardiology referral centre for the state of Victoria. All infants are outborn and transferred to RCH by a dedicated neonatal transport team, the Newborn Emergency Transport Service, Victoria, (NETS). In cases where an antenatal diagnosis of CHD has been made, infants are delivered in one of Melbourne's three tertiary neonatal centers. Following delivery and stabilsation infants are transferred to RCH for further management.

Case identification: Cases were identified from combined analysis of cardiac and NETS databases (Figure 1). Timing of diagnosis (ANdx or PNdx) was recorded, along with definitive cardiac diagnosis (obtained from post-natal echocardiogram at RCH). Demographic and treatment data, including prostaglandin E1 use (PGE_1), respiratory and cardiovascular therapies during transfer were recorded. Transport characteristics, i.e. distance and acuity of transfer (see definitions below), were also recorded, together with outcomes: length of hospital stay during first admission at RCH and survival to discharge.

Cases were excluded if they were transferred from other cardiac centers, had life threatening extra-cardiac or chromosomal anomalies, or "mild" CHD, specifically isolated atrial septal defect, ventricular septal defect, non-critical pulmonary stenosis, and patent ductus arteriosus.

Retrieval and stabilization: In Victoria, all newborn infants transferred from level 1, 2 and 3 neonatal units are retrieved and stabilised by NETS. In Victoria Level 1 centres offer birthing services to mothers with uncomplicated pregnancies and newborn infants without complications, level 2 centres

are larger hospitals which may diagnose and manage selected at risk pregnancies and neonatal conditions (excluding intensive care), and level 3 centres are large maternity and/or children's hospitals providing neonatal intensive care and sub-specialties (9). The NETS team consists of a neonatal nurse and neonatal specialist trainee, supported by a NETS consultant. After initial assessment by the NETS team, diagnosis and management plan are reviewed in a recorded teleconference with attending neonatologist and if necessary with paediatric cardiologist.

In Victoria antenatal diagnoses of CHD are typically detected at routine ultrasonographer-performed anomaly scan in the 2nd trimester. A fetal medicine specialist reviews suspicious scans and if necessary confirmed by a fetal/paediatric cardiologist. This study did not record who made the initial antenatal diagnosis. In the postnatally diagnosed group, definitive diagnosis was made by echocardiography performed by the Paediatric Cardiology Team, typically an experienced paediatric cardiology trainee and consultant paediatric cardiologist. Time at which cardiac disease was suspected during retrieval and transfer was not recorded.

Data Collection: Data were analysed using SPSS v 18. Summary statistics were used to describe the population. Comparison between groups was performed using chi-square for categorical variables and t-test or non-parametric tests for continuous variables. Subgroup analysis was performed for the three commonest cardiac diagnoses.

Ethics approval: The study was approved by the Institutional Research and Ethics committee at the Royal Children's Hospital, Melbourne.

Results

Of 320 infants with complex CHD meeting the inclusion criteria, 198 (62%) had ANdx, and 122 (38%) had PNdx. Specific diagnosis categories are provided in Table 1. There was a preponderance of univentricular cardiac malformations (hypoplastic left heart syndrome and pulmonary atresia) within the ANdx group.

Patient Characteristics

There was no significant difference in sex, birth weight or gestation between ANdx and PNdx groups, Table 2. ANdx was associated with increased rate of caesarian delivery (78 vs 32%, P=0.0001).

In the ANdx group 197 (99.5%) of infants were born at a level 3 neonatal intensive care unit, 1 was born at a level 2 special care nursery. In the PNdx group only 37 (30%) were born at a level 3 neonatal intensive care unit, the majority (70%) were born at Level 1 or 2 nurseries.

PNdx was associated with significantly higher rates of invasive ventilation (36% vs 20%, P=0.01) and higher rates of inotrope use (19% vs. 9%, P=0.007) during transport, Table 3.

163 (82.3%) infants in the ANdx category had duct dependent lesions compared to 113 (92.6%) in PNdx category. Prostaglandin E1 (PGE_1) use was significantly higher in the ANdx group (182 (91%) vs. 88 (72%), P=0.0001. Age at commencing PGE_1 was higher in the PNdx group, as was the maximum dose of prostaglandin E1, compared to the ANdx group (Table 3).

Infants with PNdx had shorter mean length of first hospital admission: mean (SD), 24(22) vs. 34(34) days (P=0.006). Survival at one year was not significantly different between ANdx and PNdx groups (83% vs. 88%). (Table 4)

We performed subgroup analysis between ANdx and PNdx for each of the three commonest diagnoses in both groups: transposition of the great arteries (TGA), aortic coarctation (CoA) and pulmonary atresia (PA). Hypoplastic left heart was common in the ANdx group but rare in the PNdx group (3 infants) preventing meaningful subgroup analysis. For each diagnosis subgroup (TGA, CoA, PA) there were no statistically significant differences in invasive ventilation rates, prostin use, inotrope use, duration of hospital stay or survival, between infants diagnosed antenatally or postnatally. The only statistically significant finding was that iNO use was higher in infants with TGA diagnosed postnatally (8/23 vs. 2/31, P=0.013).

Transport Characteristics

Average age at time of referral to the transport team (time of first telephone contact) was 15 vs. 53.4 hrs in ANdx vs. PNdx groups respectively (P<0.0001). Transfer distance in the ANdx group was median (range, aggregate) 3 (3-114, 2216) km was significantly further in the PNdx group: 84 (3-725, 10,274km), P<0.0001). All antenatally diagnosed infants were born in Melbourne, except for one infant with truncus arteriosus who delivered at a level 2 nursery approximately 110 km from RCH. All except one infant in the ANdx group were transferred by road In contrast in PNdx group, 29 (30%) were transferred by air, P<0.0001.

39% of infants in the PNdx group required highest acuity "Time Critical" transports, compared to 6% of ANdx infants (P=0.0001). Conversely only 11% of infants in the PNdx group had lowest acuity "non-urgent" transfers, compared to 24% of ANdx infants, P= 0.003.

Discussion

The findings of this study provide further evidence of the benefits of antenatal diagnosis in CHD, both to the individual infant and in terms of resource allocation and cost.

Antenatally diagnosed infants were referred earlier and transferred shorter distances, often without respiratory support or inotropes. Those diagnosed postnatally were born at non-tertiary centers, without specialist neonatal or cardiac services, presented later and required much higher levels of cardio-respiratory support during transfer from geographically distant locations.

Clinical instability in postnatally diagnosed infants with CHD is an established finding. Previous investigators have consistently observed higher levels of pre-operative acidosis, end organ dysfunction, ventricular dysfunction, ventilation and inotrope requirement in infants with PNdx compared to ANdx (5,7,11,14,15). However, these early differences in clinical status do not lead to differences in survival to hospital discharge between ANdx and PNdx group, either in our own or previous studies (3,5,7,11,16). Neurological outcome, however, may be improved by ANdx. Mahle et al have reported higher levels of adverse neurological event in postnatally diagnosed hypoplastic left

heart syndrome (8). Furthermore, Tabbutt et al observed a significant association between pre-operative intubation and impaired neurodevelopmental outcome in hypoplastic left heart syndrome (HLHS) (13). This is of particular concern in relation to our PNdx group, many more of whom required intubation and ventilation during retrieval.

The finding that hospital stay was significantly shorter in the PNdx group was surprising. This may have been due to the preponderance of univentricular anomalies, in particular HLHS, in the ANdx group. These infants undergo significant early palliative surgery during their first admission and may have extended post-operative stay before discharge.

Considering resource demands and costs associated with the timing of diagnosis, we observed that PNdx was associated with higher acuity, longer-distance transfers, more of which required air transportation. During transfer, higher rates of intensive care therapies (inotropes and ventilation) were required. Although we were not able to accurately calculate the cost associated with these, it is evident that these transfers would have been more expensive and time consuming than the transfer of ANdx infants. Copel et al previously investigated the costs of care for ANdx and PNdx infants with CHD, and observed no difference. However their study compared only the cost of inpatient care and did not include transport costs (3). Only one other study has investigated the resource requirements of transport in CHD. Jegatheeswaran et al, observed that infants with a postnatal diagnosis were 16 times more likely to require an emergency transfer, with an average transport cost of US$389 for antenatally diagnosed infants and US$5143 for postnatally diagnosed infants, in their North American cohort (4). Taking transport costs into account, improving antenatal diagnosis rates is likely to produce a significant postnatal cost saving. However, savings in postnatal transport costs must be balanced against the costs of potentially transferring and hospitalising a mother after antenatal diagnosis to ensure delivery in a centre equipped to manage the newborn with CHD.

The benefits of antenatal diagnosis, in terms of patient stability and costs, will likely vary depending on the geography and organisation of paediatric resources within a region or country. Our study was

conducted in a region where antenatally diagnosed infants predominantly deliver at one of three tertiary neonatal centers, clustered near the paediatric cardiac centre, whereas postnatally diagnosed infants may be born at very remote, geographically distant, lower-resource settings. In smaller countries, such as the UK, recent data supports a strategy of allowing antenatally diagnosed infants to be born at tertiary centers further away from a paediatric cardiac centre, providing that there is local expertise in the management of CHD and effective communication with the cardiac centre (1). This option may allow mother and infant to remain at the same site and allow for planned, less costly elective transfer only if and when required.

Our retrospective study was limited by the absence of specific cost data for each transfer, and insufficient data to compare physiological parameters (e.g. pH, lactate, saturations, blood pressure), as a measure of illness severity, between groups.

We observed higher levels of hypoplastic left heart lesions and pulmonary atresia in the antenatal group (both duct-dependent lesions likely to require univentricular surgical repair). Coarctation of aorta (CoA), meanwhile, was commoner in the PNdx group reflecting the comparative difficulty of making this diagnosis on fetal assessment. In subgroup analysis of specific diagnoses (TGA, CoA, PA) no differences in outcome between Andx and PNdx groups were observed, which may have been due to small subgroup size, or also reflect that no single diagnosis benefits from antenatal detection more than any other. It was noteworthy that iNO use was significantly higher in infants with TGA diagnosed postnatally. iNO may theoretically be disadvantageous in TGA, by increasing pulmonary blood flow and thereby reducing systemic flow. This finding highlights the importance of antenatal diagnosis not only to facilitate early initiation of beneficial therapies, but also to prevent use of potentially harmful ones.

Finally, accepting that antenatal diagnosis is beneficial to the infant and is resource efficient, how can we improve antenatal detection rates to include the one third of infants in our study whose CHD was not detected antenatally? Further analysis is required to determine where improvements can be made. It may be that better access to routine screening as part of antenatal services is required, as

well as maintaining high standards in scan quality. Additionally, new techniques or modalities in screening may be needed to ensure that those complex anomalies which are harder to detect on fetal scan can be more reliably diagnosed (6).

Conflict of interest: There are no conflicts of interest to declare

References

1. Anagnostou K, Messenger L, Yates R, Kelsall W**. (**2013) Outcome of infants with prenatally diagnosed congenital heart disease delivered outside specialist paediatric cardiac centres. Archives of disease of childhood. Fetal and neonatal edition. 98(3):F218-21.

2. Chew C, Stone S, Donath SM, Penny DJ**.** (2006) Impact of antenatal screening on the presentation of infants with congenital heart disease to a cardiology unit. Journal of paediatrics and child health. 42(11):704-8.

3. Copel JA, Tan AS, Kleinman CS**.** (1997) Does a prenatal diagnosis of congenital heart disease alter short term outcome? Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology.10(4):237-41.

4. Jegatheeswaran A, Oliveira C, Batsos C, Moon-Grady AJ, Silverman NH, Hornberger LK, Coyte P, Friedberg MK. (2011) Costs of prenatal detection of congenital heart disease. The American journal of cardiology.108(12):1808-14.

5. Kumar RK, Newburger JW, Gauvreau K, Kamenir SA, Hornberger LK**.** (1999) Comparison of outcome when hypoplastic left heart syndrome and transposition of the great arteries are diagnosed prenatally versus when diagnosis of these two conditions is made only postnatally. The American journal of cardiology. 83(12):1649-53.

6. Levy DJ, Pretorius DH, Rothman A, Gonzales M, Rao C, Nunes ME, Bendelstein J, Mehalek K, Thomas A, Nehlsen C, Ehr J, Burchette RJ,Sklansky MS. (2013) Improved prenatal detection of congenital heart disease in an integrated health care system. Pediatric cardiology. 34(3):670-9.

7. Levey A, Glickstein JS, Kleinman CS, Levasseur SM, Chen J, Gersony WM, Williams IA. (2010) The impact of prenatal diagnosis of complex congenital heart disease on neonatal outcomes. Pediatric cardiology. 31(5):587-97.

8. Mahle WT, Clancy RR, McGaurn SP, Goin JE, Clark BJ. (2001)Impact of prenatal diagnosis on survival and early neurologic morbidity in neonates with the hypoplastic left heart syndrome. Pediatrics. 107(6):1277-82.

9. Neonatal services guidelines: Defining levels of care in Victorian hospitals. http://docs.health.vic.gov.au/docs/doc/3A6EE0F0955EE151CA257B7A002448D5/$FILE/neonatal%20services%20guidelines.pdf

10. Riley M, Phyland S, Halliday J. (2004) Validation study of the Victorian Birth Defects Register. Journal of paediatrics and child health. 40(9-10):544-8.

11. Sivarajan V, Penny DJ, Filan P, Brizard C, Shekerdemian LS. (2009) Impact of antenatal diagnosis of hypoplastic left heart syndrome on the clinical presentation and surgical outcomes: the Australian experience. Journal of paediatrics and child health. 45(3):112-7.

12. Stoll C, Alembik Y, Dott B, Meyer MJ, Pennerath A, Peter MO, De Geeter B.(1998) Evaluation of prenatal diagnosis of congenital heart disease. Prenatal diagnosis. 18(8):801-7.

13.Tabbutt S, Nord AS, Jarvik GP, Bernbaum J, Wernovsky G, Gerdes M, Zackai E, Clancy RR, Nicolson SC, Spray TL, Gaynor JW (2008) Neurodevelopmental outcomes after staged palliation for hypoplastic left heart syndrome. Pediatrics.121(3):476-83.

14. Tworetzky W, McElhinney DB, Reddy VM, Brook MM, Hanley FL, Silverman NH. (2001) Surgical outcome after fetal diagnosis of hypoplastic left heart syndrome. Circulation. 103(9):1269-73.

15. Verheijen PM, Lisowski LA, Stoutenbeek P, Hitchcock JF, Brenner JI, Copel JA, Kleinman CS, Meijboom EJ, Bennink GB.(2001) Prenatal diagnosis of congenital heart disease affects preoperative acidosis in the newborn patient. The Journal of thoracic and cardiovascular surgery. 121(4):798-803.

16. Yeager SB, Horbar JD, Greco KM, Duff J, Thiagarajan RR, Laussen PC. (2006) Pretransport and posttransport characteristics and outcomes of neonates who were admitted to a cardiac intensive care unit. Pediatrics. 118(3):1070-7.

Table 1: Nature of congenital cardiac lesions in Antenatal and Postnatal diagnosis groups.

		Antenatal Diagnosed N=198	Postnatal Diagnosed N=122
Left heart obstruction	Aortic stenosis	2	11
	Coarctation of aorta	13	26
	Hypoplastic Left Heart Syndrome	71	3
	Interrupted Aortic Arch	7	4
	Hypoplastic arch	0	8
Right heart obstruction	Critical Pulmonary Stenosis	1	9
	Ebstein's anomaly	2	4
	Pulmonary atresia	29	11
	Tricuspid Atresia	4	0
	Tetralogy of Fallots	15	7
Mixing defects	TGA	32	23
	Truncus arteriosus	3	2
	Total anomalous pulmonary venous drainage	0	7
Miscellaneous	Cor Triatriatum	0	1
	Heterotaxy syndrome	1	0
	Complex cardiac anatomy	2	0
	Atrioventricular septal defect	4	1
	Double Outlet Right Ventricle	6	5
	Double Outlet Right Ventricle with Transposition of great arteries	4	0
	Double Outlet Right Ventricle with Hypoplastic Left Heart Syndrome	2	0

Table 2: Demographic data

	Antenatally diagnosed N=198	**Postnatally diagnosed N=122**	**P value**
Gestation (mean, SD)	39 (2)	39 (2)	0.43
Birth weight (mean, SD)	3.1 (0.6)	3.2 (0.7)	0.27
Male, n (%)	134 (68)	70 (57)	0.06
Caesarian section, n (%)	154 (78)	39 (32)	0.0001
IUGR, n (%)	24 (12)	18 (15)	0.5

Table 3: Transport Characteristics

	Antenatally diagnosed N=198	**Postnatally diagnosed N=122**	**P value**
Transport category			
Time critical, n (%)	11 (6)	48 (39)	0.0001
Primary urgent, n (%)	139 (70)	61 (50)	0.0001
Non-urgent, n (%)	48 (24)	13 (11)	0.003
Road / air transport	197/1	93/29	<0.0001
Distance (median, range)	3 (3-114)	84 (3-725)	<0.0001
Respiratory status during transport			
Self-ventilating, n (%)	150 (76)	77 (62)	0.016
CPAP, n (%)	9 (4)	2 (2)	
IMV, n (%)	39 (20)	44 (36)	0.001
Cardiac therapies during transport			
PGE_1, n (%)	184 (93)	86 (70)	0.0001
Time to receive PGE_1, hours (mean, SD)	3.2 (14.5)	37 (63)	<0.0001
Max PGE_1 dose, ng/kg/min (mean, SD)	14 (13.7)	26 (31.3)	0.0003
Inotropes	17 (9)	23 (19)	0.007

CPAP- Continuous Positive Airway Pressure, IMV- Invasive Mandatory Ventilation

Table 4: Outcome

	Antenatally diagnosed N=198	**Postnatally diagnosed N=122**	**P value**
Length of stay during 1st admission, days (mean, SD)	34 (34)	24 (22)	0.006
Survival at 1 year	156 (83)	106 (88)	0.26

Figure 1: Flowchart of case identification and categorization