Congenital left heart obstruction: ethnic variation in incidence and infant survival

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ABSTRACT

Objective To investigate the relationship between ethnicity and health outcomes among fetuses and infants with congenital left heart obstruction (LHO).

Design A retrospective population-based review was conducted of fetuses and infants with LHO including all terminations, stillbirths and live births from 20 weeks' gestation in New Zealand over a 9-year period. Disease incidence and mortality were analysed by ethnicity and by disease type: hypoplastic left heart syndrome (HLHS), aortic arch obstruction (AAO), and aortic valve and supravalvular anomalies (AVSA).

Results Critical LHO was diagnosed in 243 fetuses and newborns. There were 125 with HLHS, 112 with AAO and 6 with isolated AVSA. The incidence of LHO was significantly higher among Europeans (0.59 per 1000) compared with Māori (0.31 per 1000; p<0.001) and Pacific peoples (0.27 per 1000; p=0.002). Terminations were uncommon among Māori and Pacific peoples. Total case fatality was, however, lower in Europeans compared with other ethnicities (42% vs 63%; p=0.002) due to a higher surgical intervention rate and better infant survival. The perinatal and infant mortality rate was 82% for HLHS, 15% for AAO and 2% for AVSA.

Conclusion HLHS carries a high perinatal and infant mortality risk. There are ethnic differences in the incidence of and mortality from congenital LHO with differences in mortality rate suggesting inequities may exist in the perinatal management pathway.

What is already known on this topic?

- Congenital left heart obstruction can result in acute cardiovascular compromise and death if not detected and treated early.
- This group of anomalies present diagnostic and treatment challenges.
- There are ethnic differences in survival patterns among New Zealand's main ethnic groups.

What this study adds?

- The incidence of and mortality from congenital left heart obstruction varies by ethnicity.
- Perinatal management pathways vary among ethnic groups.
- Hypoplastic left heart syndrome carries a high mortality risk despite early diagnosis and treatment.

INTRODUCTION

Congenital malformations are the leading cause of infant mortality in the developed world, and approximately 40% of these deaths are attributed to congenital cardiac disease (CHD).[1 2] Obstructive left heart lesions have been identified as the group of cardiac anomalies most likely to cause death in infancy.[3] These defects are usually duct dependent for systemic blood flow; therefore, unrecognised disease in the newborn can result in rapid cardiovascular compromise and death. Routine newborn physical examination seldom yields abnormal findings in these babies in the first 24–48 hours when the ductus arteriosus is patent.[4] The poor postnatal detection rate means that failure to make an antenatal diagnosis is associated with an increased infant mortality.[5]

A population-based review was undertaken to evaluate the incidence and impact of left heart obstruction (LHO) on our community with a specific focus on the variation in health outcomes in New Zealand's three major ethnic groups, namely: European; Māori and Pacific peoples.

METHODS

This study of infants and fetuses with critical LHO in New Zealand between February 2006 and December 2014 included those with hypoplastic left heart syndrome (HLHS), coarctation of the aorta (CoA), interrupted aortic arch (IAA) and aortic valve and supravalvular anomalies (AVSA). CoA and IAA are, for the purpose of this review, collectively referred to as aortic arch obstruction (AAO). Critical defects were defined as those resulting in death of the fetus or neonate, or requiring intervention in the first 28 days after birth. The study included all births from 20 weeks' gestational age including live-born infants, stillbirths and pregnancy terminations. Those with associated extracardiac and chromosomal anomalies were included as were multiple gestations.

New Zealand has a single paediatric cardiac centre based in Auckland. Study participants were identified from cardiac surgery and cardiology databases, including the national fetal cardiology dataset, the latter including all fetuses referred for a cardiology opinion. Mortality data were obtained from the Perinatal and Maternal Mortality Review Committee (PMMRC) and the Child and Youth Mortality Review Committee (CYMRC). Participants were identified from these data sources based

Table 1 Incidence by ethnicity

	European	Māori	IRR (95% CI)	P value: European/Māori	Pacific peoples	IRR (95% CI)	P value: European/Pacific	Other	IRR (95% CI)	P value: European/other	All
Total births, n (%)	270 031 (48)	151 335 (27)			63 248 (11)			76 612 (14)			
Cardiac anomaly, n (per 1000):											
All LHO	159 (0.59)	48 (0.31)	1.86 (1.34 to 2.56)	<0.001	17 (0.27)	2.19 (1.33 to 3.61)	0.002	19 (0.25)	2.37 (1.48 to 3.82)	<0.001	243 (0.43)
HLHS	76 (0.28)	26 (0.17)	1.64 (1.05 to 2.56)	0.03	10 (0.16)	1.78 (0.92 to 3.44)	0.08	13 (0.17)	1.66 (0.92 to 2.99)	0.08	125 (0.22)
AAO	78 (0.29)	21 (0.14)	2.08 (1.29 to 3.37)	0.003	7 (0.11)	2.61 (1.20 to 5.66)	0.01	6 (0.08)	3.69 (1.61 to 8.46)	<0.001	112 (0.20)
AVSA	5 (0.02)	1 (0.01)	2.80 (0.33 to 23.98)	0.3	0		NE	0		NE	6 (0.01)
Deaths per 1000	0.25	0.18	1.39 (0.89 to 2.17)	0.1	0.16	1.57 (0.81 to 3.05)	0.2	0.21	1.18 (0.69 to 2.05)	0.5	0.21

AAO, aortic arch obstruction; AVSA, aortic valve and supravalvular anomalies; HLHS, hypoplastic left heart syndrome; IRR, incidence rate ratio; LHO, left heart obstruction; NE, not estimable.

on the Perinatal Society of Australia and New Zealand Perinatal Death Classification system[6] (for PMMRC data) and International Classification of Diseases, 10th Revision codes (for CYMRC data). Patient numerator and denominator demographic data were obtained from the Ministry of Health's National Maternity Collection. Data from each database were merged using mother and/or baby National Health Index numbers as a unique identifier. Hospital records were reviewed to ascertain the timing of diagnosis and to supplement data missing from other sources.

Diagnostic categories

HLHS: a spectrum of cardiac malformations characterised by significant hypoplasia of the left ventricle including atresia or stenosis of the aortic and/or mitral valve and hypoplasia of the aortic arch. Cases with an unbalanced atrioventricular canal defect were excluded.

AAO: CoA or IAA (with or without associated aortic arch hypoplasia) occurring in isolation or in conjunction with the following cardiac anomalies: ventricular septal defects, atrial septal defects, mitral and aortic valve anomalies and/or a left superior vena cava. AAO occurring in association with left ventricular hypoplasia was classified as HLHS.

AVSA: stenosis of the aortic valve or supravalvular region occurring in isolation or in conjunction with cardiac defects such as ventricular septal defect (VSD), atrial septal defect (ASD) or mitral valve anomalies.

Those with malpositioned great arteries were excluded from all groups.

Ethnicity data

Established practice for the collection of ethnicity data in New Zealand entails self-identified ethnicity—in case of a minor ethnicity is identified by the parents of the child. If an individual identifies with more than one ethnic group, a single ethnicity is assigned using a prioritisation system,[7] with priority given to Māori (the indigenous people) followed by Pacific peoples (those born or with self-identified descent from the islands of the South Western Pacific). All other groups receive priority over European. In this study, ethnic groups other than European, Māori and Pacific peoples were classified as 'other'. In some analyses, ethnicity data were further categorised into two groups: European and non-European.

Statistical analysis

Median and range were used to describe continuous variables, and percentages were used for categorical variables. Incidence rate ratios and 95% CIs were calculated and are presented for all ethnicities. The χ^2 was used for comparisons between categorical variables, and Fisher's exact t test was used to compare continuous variables. All p values are two tailed. Data were analysed using statistical software (JMP, V.14.0).

RESULTS

Between February 2006 and December 2014, there were a total of 561 226 live births, stillbirths and pregnancy terminations (from 20 weeks' gestational age) in New Zealand. Of those, 556 902 infants were born alive. Critical LHO was diagnosed in a total of 243 fetuses and newborn infants, giving an incidence of 0.43 per 1000 total births and terminations combined. Of these, there were 125 with HLHS, 112 with AAO and 6 with an isolated aortic valve anomaly (table 1). There were 137 males (incidence 0.5 per 1000 males) and 106 females (0.4 per 1000 females; p=0.1). The incidence of LHO was higher among Europeans

Table 2 Antenatal diagnosis rate by diagnostic category

	HLHS	AAO	AVSA	All	P value
Antenatal diagnosis					
All	114/125 (91)	34/112 (30)	2/6 (33)	150/243 (62)	<0.001
No other anomaly	98/108 (91)	25/93 (27)	2/6 (33)	125/207 (60)	<0.001
Chromosomal or major extracardiac anomaly	16/17 (94)	9/19 (47)	–	25/36 (69)	0.002
P value	0.6	0.08	n/a	0.3	

AAAO, aortic arch obstruction; AVSA, aortic valve and supravalvular anomalies; HLHS, hypoplastic left heart syndrome; n/a, not applicable.

compared with Māori (p<0.001), Pacific peoples (p=0.002) and other ethnicities (p<0.001). The incidence ranged from 0.59 to 0.25 per 1000 (table 1). The difference was most marked for AAO. Critical AVSA was uncommon among all groups.

Overall, 150 (62%) were diagnosed in the antenatal period. Antenatal detection rates were associated with diagnostic category with HLHS more likely to be diagnosed before birth (91%) than either AAO (30%) or AVSA (33%) (p<0.001). A chromosomal or major extracardiac anomaly was present in 17% of those with AAO and 14% with HLHS and did not significantly improve the odds of antenatal detection in either group (table 2). Ethnicity did not have an impact on antenatal detection rates (table 3). There was, however, a difference in the timing of antenatal detection with Europeans diagnosed at a median (range) gestation of 22 weeks (18–38) compared with 29 (19–38) for Māori, 30 (23–37) for Pacific peoples and 24 (18–28) for other ethnicities (p=0.001).

The total number of deaths was 120. The overall LHO-specific perinatal and infant mortality rate for the period 2006–2014 was 0.21 per 1000 total births. Mortality to 1 year of age was associated with both the type of cardiac anomaly and ethnicity (table 4).

There were 72 fetal deaths. Fifty-seven were attributed to pregnancy termination; fifty-five with HLHS and two with AAO. Termination rates varied by ethnicity (table 4). There were no terminations recorded among Pacific peoples. The highest termination rate was found among New Zealand's other ethnic groups (12/19, 63%). Pregnancy termination occurred at a median gestation of 22 weeks (range 20–27).

There were 15 stillbirths that occurred between 22 weeks' gestational age and 37 weeks' gestational age (median 32). Twelve had HLHS and three had AAO, equating to a stillbirth rate of 10% for HLHS and 3% for AAO (p=0.03). The rate of stillbirths was highest among Pacific women (4/17, 24%), greater than in all other ethnic groups (p=0.01). The overall fetal death rate was highest for New Zealand's other ethnic groups as a result of the high termination rate (p=0.01).

Forty-eight deaths occurred after birth. Seventeen (29%) live-born infants with HLHS received palliative care. Four (4%) infants with AAO received palliative care; all had major comorbidities. Mortality after surgical intervention was influenced by the type of defect, with HLHS carrying a higher mortality rate compared with other anomalies (p<0.001). Eighteen of 41 (44%) infants with HLHS died in the first year despite an intention to provide active treatment. Fifteen of these deaths occurred after surgical intervention took place. Contrary to this, deaths more often occurred prior to intervention among those infants who died with AAO (table 4). There was one death in the AVSA group: a case of supravalvular aortic stenosis with sudden death at 28 days of age. Abnormal coronary arteries were found at postmortem examination (table 4). Infant mortality was far lower in Europeans (21/113, 19%) compared with all other non-European ethnicities (27/58, 47%; p<0.001). Active treatment was provided more often if live-born infants with LHO were European (109/113; 96%) compared with 42/58 (72%) non-Europeans; p<0.001 (figure 1). This was also true for the HLHS subgroup where 28/32 (88%) live-born European infants received active treatment in comparison with 13/26 (50%) of those from other non-European ethnic groups (p=0.002). In those where treatment was provided, mortality in the non-European group was higher (p=0.1).

The total case fatality was lower in Europeans compared with the other three ethnic groups (42% vs 63%; p=0.002) (figure 1). The higher incidence of LHO among Europeans did, however, result in a higher overall mortality rate for this group (0.25 per 1000) compared with non-Europeans (0.18 per 1000; p=0.1).

DISCUSSION

In this population-based study, we have demonstrated a marked difference in the incidence of left heart anomalies among ethnic groups. Furthermore, ethnic disparities in health outcomes were apparent in the case fatality rate as highlighted by the difference in pregnancy outcomes, palliative care rates and, to a lesser extent, the difference in mortality among cases where there was an intention to pursue active treatment.

The rate of LHO among Europeans in New Zealand is similar to that reported in other Caucasian populations,[8–10] but a low incidence of LHO was seen among Māori and Pacific peoples. Several studies have reported low rates of LHO in African-Americans compared with Europeans.[11–13] A low incidence of left heart lesions is also seen in Asians.[14 15] Ethnic differences in incidence suggest a strong genetic component to the development of these malformations. Familial clustering has been associated

Table 3 Antenatal diagnosis rate by ethnicity

	European	Māori	Pacific peoples	Other	All	P value
Antenatal diagnosis						
All LHO	93/159 (59)	31/48 (65)	11/17 (65)	15/19 (79)	150/243 (62)	0.3
HLHS	69/76 (91)	24/26 (92)	8/10 (80)	13/13 (100)	114/125 (91)	0.4
AAO	23/78 (29)	6/21 (29)	3/7 (43)	2/6 (33)	34/112 (30)	0.9
AVSA	1/5 (20)	1/1 (100)	0	0	2/6 (33)	NE

AAO, aortic arch obstruction; AVSA, aortic valve and supravalvular anomalies; HLHS, hypoplastic left heart syndrome; LHO, left heart obstruction; NE, not estimable.

Table 4 Mortality by diagnostic category and ethnicity

Total cases	All n=243	HLHS n=125	AAO n=112	AVSA n=6	P value*	European n=159	Māori n=48	Pacific peoples n=17	Other n=19	P value†
Fetal deaths, n (%)	72 (30)	67 (54)	5 (4)	–	<0.001	46 (29)	10 (21)	4 (24)	12 (63)	0.01
Termination	57 (23)	55 (44)	2 (2)	–	<0.001	39 (25)	6 (13)	–	12 (63)	<0.001
Stillbirth	15 (6)	12 (10)	3 (3)	–	0.03	7 (4)	4 (8)	4 (24)	–	0.01
All live-born infants	n=171	n=58	n=107	n=6		n=113	n=38	n=13	n=7	
Palliative care, n (%)	21 (12)	17 (29)	4 (4)	–	<0.001	5 (4)	10 (26)	3 (23)	3 (43)	<0.001
Active treatment, n (%)	150 (88)	41 (71)	103 (96)	6 (100)	<0.001	108 (96)	28 (74)	10 (77)	4 (57)	<0.001
Preoperative death	9 (6)	3 (7)	5 (5)	1 (17)	0.4	5 (5)	2 (7)	1 (10)	1 (25)	0.7
Postoperative death	18 (12)	15 (37)	3 (3)	–	<0.001	11 (10)	5 (18)	2 (20)	–	
Neonatal and infant deaths, n (%)	48 (28)	35 (60)	12 (11)	1 (17)	<0.001	21 (19)	17 (45)	6 (46)	4 (57)	<0.001
Deaths where treatment intended	27/150 (18)	18/41 (44)	8/103 (8)	–	<0.001	16/109 (15)	7/28 (25)	3/10 (30)	1/4 (25)	0.4
All deaths, n (%)	120 (49)	102 (82)	17 (15)	1 (17)	<0.001	67 (42)	27 (56)	10 (59)	16 (84)	0.003

*P value comparing all types of anomalies.
†P value comparing all ethnic groups.
AAO, aortic arch obstruction; AVSA, aortic valve and supravalvular anomalies; HLHS, hypoplastic left heart syndrome.

with bicuspid aortic valves and HLHS. There is a well-recognised recurrence risk associated with left heart lesions. The frequency of cardiovascular malformations in first-degree relatives of a proband with HLHS is 10%–19%.[16–18] With both an affected parent and sibling, the risk is greater, estimated at 26%.[16]

An antenatal diagnosis of a cardiac anomaly enables clinicians to counsel parents allowing them an opportunity to make an informed decision around pregnancy and postnatal management. Midtrimester fetal ultrasound anatomy screening is available for pregnant women in New Zealand between 18 weeks' gestation and 21 weeks' gestation. The prescribed protocol includes an assessment of the fetal heart[19]; however, the antenatal detection of critical CHD varies significantly. Factors that impact on the sensitivity of this screening tool include: operator skill and experience[20 21]; maternal habitus[22 23]; the setting in which screening is undertaken[24 25]; the type of cardiac defect; and the presence of extra-cardiac anomalies.[26–28] In keeping with other studies, we report a substantial difference in the antenatal detection rate of HLHS compared with other left heart anomalies.[26 27 29] Ventricular disproportion is evident on a four-chamber view of the fetal heart, and HLHS is therefore more readily detected than anomalies that may only be visualised with extended outflow tract views. Among fetuses with AAO, a marginally higher antenatal detection rate was seen when extracardiac anomalies were present in conjunction with the cardiac malformation.

Most commonly a diagnosis of isolated AAO or an AVSA is associated with a favourable outcome,[5 30] and accordingly, most clinicians and parents would consider a path of active intervention. This may not be the case with a single-ventricle circulation such as HLHS given the poorer outcomes reported for this group. Pregnancy termination rates are influenced by this and various other factors. In keeping with other literature we report higher pregnancy termination rates in the context of complex cardiac disease and when there is an associated chromosomal or extracardiac anomaly.[31 32] Early diagnosis also has been associated with higher termination rates[33] as local laws may prevent termination of a pregnancy at an advanced gestation. Pacific women are more likely to initiate antenatal care late in pregnancy comparative with all other ethnic groups in New Zealand.[34] Pacific women are also more likely than other groups to have less effective antenatal care with, for example, lower rates of best practice screening despite the high rate of obesity in this group being associated with adverse pregnancy outcomes.[35] 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 an anomaly will be seen by specialist services prior to 20 weeks' gestation to discuss management options.

These findings indicate a lower pregnancy termination rate among Māori and Pacific peoples and a difference in management options taken after the birth of an affected infant. One-year survival among live-born European infants was higher compared with that of non-Europeans in the context of significant differences in the proportion of infants for whom there was a plan for active intervention (96% of live-born European infants compared with 72% of live-born non-European infants). There are a number of possible explanations for this difference, including what and how treatment options are presented to different ethnic groups, the level of understanding when there is limited health literacy or when English is not the first language and also how the information is dealt with in the context of cultural and religious beliefs. Unconscious racial bias among healthcare providers has been shown to impact on the treatment

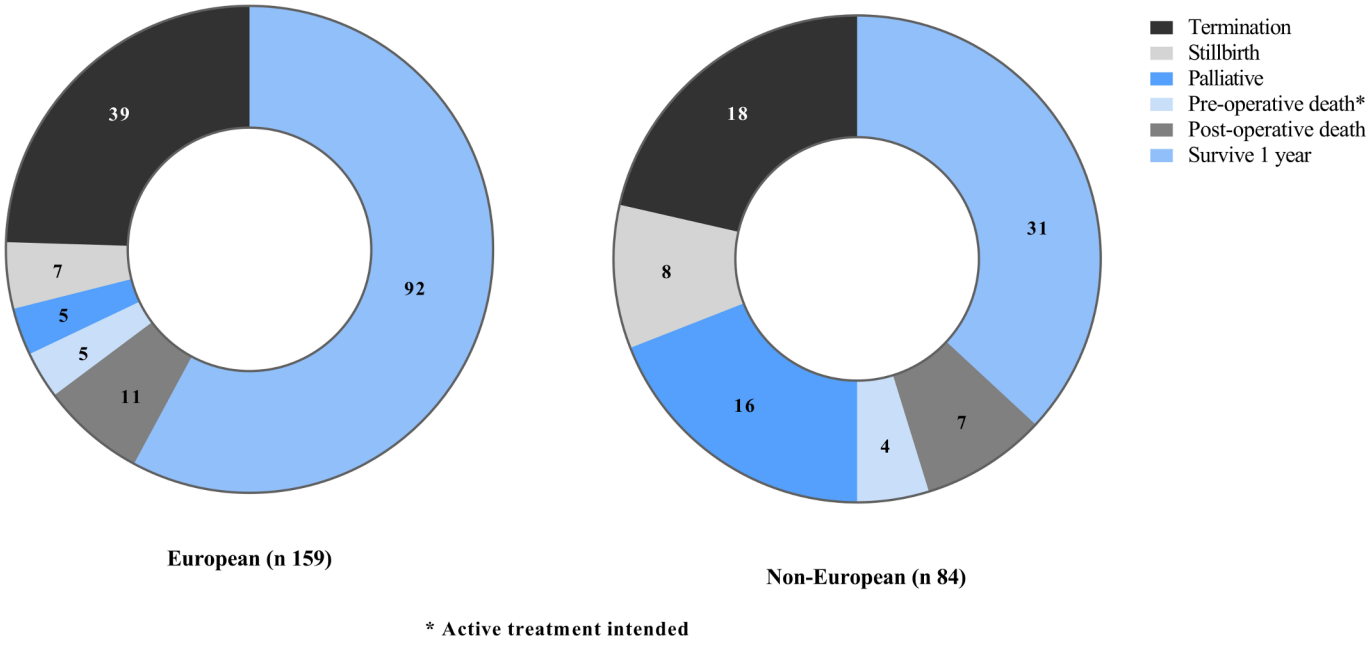

Figure 1 Outcomes: European vs non-European.

offered to patients, with minority ethnic groups receiving lower quality treatment.[36 37] In New Zealand is has been shown that Māori are less likely to receive curative treatment for cancer and are more likely to experience a delay in treatment initiation compared with non-Māori.[38 39] The potential impact of religious and cultural beliefs should be considered also as termination may be less acceptable in some communities.

Māori and Pacifica experience inequities across all indicators of health status and access to health services in New Zealand.[40] The rural nature of many Māori communities makes access to specialist healthcare services particularly difficult,[41] which may contribute to the higher infant mortality rate seen among non-Europeans receiving active treatment. However, the higher number of pregnancy terminations among Europeans, particularly in the context of anomalies with a poor prognostic outlook, is likely to be a contributing factor to the observed inequity.

The stillbirth rate was associated with ethnicity, in keeping with other ethnic disparities observed in this study. It was also associated with the type of cardiac defect. Placenta-related complications in women carrying a fetus with complex cardiac disease have been described in the past. The rate of pre-eclampsia, intrauterine growth restriction and stillbirths has previously been reported to be higher in this group compared with the normal population.[42 43]

CONCLUSION

There is significant ethnic variation in disease incidence. The lower rate of pregnancy terminations and higher rate of palliative care among Māori and Pacific peoples may reflect bias in counselling or could be reflective of an interaction between ethnicity and disease severity, with the more severely affected European fetuses undergoing termination. The same type of abnormality in Māori and Pacifica could have a higher risk of stillbirth or be more likely to follow a palliative care pathway after birth. However, it would be expected that when adding death from termination of pregnancy to stillbirth, death with palliative care and postsurgical death, that case fatality would be the same across ethnicities or lower among ethnicities undertaking fewer terminations. This was not the case, suggesting that implicit bias may be a contributor. Further research is needed to better understand where these inequities have arisen. These factors may have important implications when interpreting postnatal outcome studies especially when ethnicity appears to be associated with outcome. The complete spectrum of perinatal and neonatal care should be considered when assessing the impact of intervention on survival.

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Contributors EC conceptualised and designed the study, carried out the analysis, drafted the initial manuscript and reviewed and revised the manuscript. TG, LS and FHB assisted with the design of the study, provided supervision over all aspects of the study and reviewed and revised the manuscript. SC and TP reviewed and revised the manuscript and provided guidance with the interpretation of data related to Maori and Pacifica. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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