

Cardiovascular Malformations Among Preterm Infants

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ABSTRACT. *Objective.* Preterm birth and cardiovascular malformations are the 2 most common causes of neonatal and infant death, but there are no published population-based reports on the relationship between them. We undertook this study to determine the prevalence and spectrum of cardiovascular malformations in a preterm population, the prevalence of prematurity among infants with cardiovascular malformations, and the influence of prematurity and cardiovascular malformations on outcomes.

Methods. We based the study on the population of the former Northern Health Region of England. We identified all live-born infants with cardiovascular malformations diagnosed in the first 1 year of life from the regional pediatric cardiology database, which includes the gestational age and details of the diagnosis. We limited ascertainment to malformations diagnosed by the age of 12 months. Infants with isolated patent ductus arteriosus or atrial septal defect were excluded, to avoid ascertainment bias. Infants with ventricular septal defect were classified according to whether they required surgery in the first 1 year. There are no population data on gestational ages for all births in our population for the era of this study; therefore, we used data published in the literature for populations similar to our own to predict that 0.4% of live births occur at <28 weeks of gestation, 0.9% at 28 to 31 weeks, and 6% at 32 to 36 weeks. Overall, 7.3% of live-born infants are preterm.

Results. Of 521 619 live-born infants in 1987–2001, 2964 had cardiovascular malformations (prevalence: 5.7 cases per 1000 live births). Cardiovascular malformations were present at 5.1 cases per 1000 term infants and 12.5 cases per 1000 preterm infants. The odds ratio (OR) for a cardiovascular malformation in prematurity was 2.4 (95% confidence interval [CI]: 2.2–2.7). We found that 474 infants (16%) with cardiovascular malformations were born at <37 weeks of gestation, giving an OR for prematurity among infants with a cardiovascular malformation of 2.4 (95% CI: 2.2–2.7). More infants were born preterm with diagnoses of pulmonary atresia with ventricular septal defect (23%), complete atrioventricular septal defect (22%), and coarctation of the aorta, tetralogy of Fallot, and pulmonary valve stenosis (each 20%). Fewer were born preterm with diagnoses of pulmonary atresia and intact ventricular septum (7%), transposition of the great arteries (8%), and single ventricle (9%). We found that 18% of infants with ventricular septal defect requiring surgery were preterm, compared with 13% in the nonsurgical

group. Preterm infants with ventricular septal defect required surgery in 30% of cases, compared with 23% of term infants with ventricular septal defect. These figures show that the excess of cardiovascular malformations among preterm infants cannot be explained by greater ascertainment of minor ventricular septal defects. In our denominator population, 646 live-born infants were recognized as having trisomy 21, and gestational age data were available for 609. Of these, 149 (25%; 95% CI: 21–28%) were preterm. Approximately two thirds of infants with complete atrioventricular septal defect have trisomy 21. Complete atrioventricular septal defect was no more common among preterm infants with trisomy 21 (16%) than among term infants with trisomy 21. However, the increased incidence of prematurity among infants with trisomy 21 probably explains some of the excess of preterm births among infants with complete atrioventricular septal defect. Only 4 (11%) of 38 infants with 22q11 deletion were born preterm. None of those infants had pulmonary atresia with ventricular septal defect; therefore, 22q11 deletion does not explain the excess of preterm births in pulmonary atresia with ventricular septal defect. The OR for death in the first 1 year in the presence of a cardiovascular malformation was 4.4 (95% CI: 3.1–5.5) overall; ORs were 1.8 at <28 weeks of gestation, 3.7 at 28 to 31 weeks, 11.0 at 32 to 36 weeks, and 35.6 at term.

Conclusions. This study showed that preterm infants have more than twice as many cardiovascular malformations as do infants born at term and that 16% of all infants with cardiovascular malformations are preterm. It also showed, not surprisingly, that there is an increased mortality rate among infants born preterm with a cardiovascular malformation. The additional effect of cardiovascular malformations on mortality rates is most marked for term and near-term infants, for whom mortality rates are otherwise low. The excess of cardiovascular malformations among preterm infants is intriguing but not easy to explain. Previous studies of birth weight among infants with cardiovascular malformations reported a significant increase in the likelihood of being small for gestational age among infants with tetralogy of Fallot, complete atrioventricular septal defect, hypoplastic left heart, or large ventricular septal defect. There is an obvious relationship between birth weight and gestational age, and those studies also showed an increased prevalence of prematurity among infants with tetralogy of Fallot, pulmonary stenosis, aortic stenosis, coarctation of the aorta, complete atrioventricular septal defect, or ventricular septal defect. There is also a high prevalence of cardiovascular malformations among late stillbirths, with major differences in the number and spectrum of cardiovascular malformations, compared with those seen in postnatal life. In particular, there is a greater incidence of coarctation of the aorta, double-inlet left ventricle, hypoplastic left heart, truncus arteriosus, double-outlet right ventricle, and atrioventricular septal defect among stillbirths. This spectrum of malformations is similar to that in our study and to those in other reports. Whether

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Accepted for publication Jun 24, 2005.

doi:10.1542/peds.2005-0397

No conflict of interest declared.

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the increased prevalence of cardiovascular malformations among preterm infants and the increase in stillbirths suggest clues to the cause is difficult to say. The influence of preterm birth should be taken into account in risk assessment and risk stratification for surgical repair. *Pediatrics* 2005;116:e833–e838. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2005-0397; cardiovascular malformation, prematurity.

ABBREVIATIONS. OR, odds ratio; CI, confidence interval.

Cardiovascular malformations affect ~6 to 8 infants per every 1000 live births.¹ Cardiovascular malformations and prematurity are the 2 most common causes of neonatal and infant death, but there are no published population-based reports of the relationship between them.^{2,3} We undertook this study to determine the prevalence and spectrum of cardiovascular malformations in a preterm population, the prevalence of prematurity among infants with cardiovascular malformations, and the influence of prematurity and cardiovascular malformations on outcomes.

METHODS

Population Base

We based this study on the population of the former Northern Health Region of England, which includes North and East Cumbria, Northumberland, Tyne and Wear, Durham, and Cleveland. All infants with suspected cardiovascular malformations are referred to a single pediatric cardiology center. The population of ~3 million is stable and geographically well defined. The recent average annual live birth rate has been ~35 000 births per year. The ethnic composition of the population is 97.6% white, 0.1% black, 1.5% Asian, 0.5% mixed, and 0.3% other.⁴

We included all live-born infants with cardiovascular malformations diagnosed in the first 1 year of life. The infants were identified from the regional pediatric cardiology database, which includes the gestational age and details of the diagnosis. The database has had prospective ascertainment since 1990, with retrospective ascertainment back to 1985.⁵

Case Definition

In common with most previous epidemiologic studies, we defined a cardiovascular malformation as “a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional importance.”⁶ We limited ascertainment to malformations diagnosed by the age of 12 months. Although most significant heart disease has presented by this time, relatively few cases of patent ductus arteriosus and atrial septal defect are diagnosed in the first 1 year.⁷ Therefore, both of these diagnoses were excluded, to avoid ascertainment bias, particularly because preterm infants are more likely to have patent ductus arteriosus and are more likely to undergo echocardiography in a NICU. We also excluded from the study infants with physiologic pulmonary artery branch stenosis, patent foramen ovale, isolated cardiac arrhythmia, isolated bicuspid aortic valve, mitral valve prolapse without regurgitation, isolated dextrocardia, and cardiac tumors. Because of their relative rarity, we grouped together under the diagnostic label “single ventricle” infants with mitral atresia, tricuspid atresia, and double-inlet left ventricle. Ventricular septal defects were classified according to whether they required surgery in the first 1 year. This subanalysis was limited to surviving infants because the contribution of the ventricular septal defect to death could not be determined retrospectively, especially for preterm infants. Analysis of ventricular septal defects including deaths yielded findings very similar to those described below.

We defined gestational age as the number of completed weeks from the first day of the mother’s last menstrual period to the day of delivery. If the menstrual history was in doubt, then gestational

age was estimated from obstetric assessments, including physical examination and ultrasonography.⁸

The Northern Congenital Abnormality Survey provided data on the numbers of live births and total infant mortality rates.⁹ There are no data for our population on the gestational age at birth for all infants or on total infant mortality rates according to gestational age. To be able to predict the size of the denominator groups, we plotted data for populations similar to our own described in the literature^{10–13} and in the All Wales Perinatal Survey (1993–2000)¹⁴ (Fig 1). Data points from the various publications were given equal weight and, from the line of best fit in Fig 1, we predicted that 0.4% of live births occur at <28 weeks of gestation, 0.9% at 28 to 31 weeks, and 6% at 32 to 36 weeks. Therefore, overall 7.3% of live-born infants are preterm. Some of these studies also provided data on the relationship between preterm birth and mortality rates.^{10,11} The study was approved by the Newcastle and North Tyneside Local Research Ethics Committee.

Statistical Analyses

We limited statistical analysis to calculation of odds ratios (ORs) and their associated confidence intervals (CIs)¹⁵ and comparisons of proportions with the χ^2 test.

RESULTS

Cardiovascular Malformations Among Preterm Infants

Of 521 619 live births in the study population in 1987–2001, 2964 infants were recognized as having a cardiovascular malformation (excluding atrial septal defect and patent ductus arteriosus) in infancy (Table 1). This gives a prevalence of 5.7 cases per 1000 live births. With our assumption that 7.3% of all live births are preterm, the prevalence at live birth of cardiovascular malformations among preterm infants was 12.5 cases per 1000 live births. In comparison, cardiovascular malformations were present at 5.1 cases per 1000 term infants, giving an OR for cardiovascular malformations in prematurity of 2.4 (95% CI: 2.2–2.7). Cardiovascular malformations

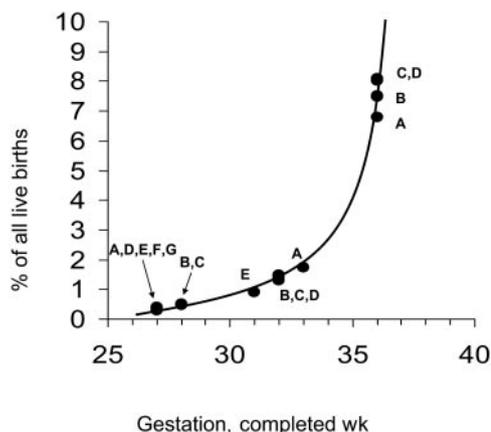


Fig 1. Prevalence of live births at various gestational ages of <37 weeks in 5 publications regarding populations similar to our own. Data points represent estimates of frequency at less than the indicated gestational age. The reports show sufficient consistency for us to derive predictions of the prevalence of preterm birth at <28 weeks, <32 weeks, and <37 weeks from the line of best fit. We assumed that 0.4% of live births in our own denominator population were at <28 weeks, 0.9% at 28 to 31 weeks, and 6.0% at 32 to 36 weeks and thus the cumulative prevalence of preterm birth was 0.4% at <28 weeks, 1.3% at <32 weeks, and 7.3% at <37 weeks. Data points are as follows: A, Joseph et al,¹² 1992–1994; B, Centers for Disease Control and Prevention,¹³ 1989; C, Centers for Disease Control and Prevention,¹³ 1996; D, Alexander et al,¹⁰ 1995–1997; E, All Wales Perinatal Survey,¹⁴ 1993–2000; F, Tin et al,¹¹ 1987–1990; G, Tin et al,¹¹ 1991–1994.

TABLE 1. Proportion of Live-Born Infants and Prevalence at Live Birth of Cardiovascular Malformations in Each Gestational Age Group

Gestational Age, wk	No. (%; 95% CI)	
	Live Births	Infants With Cardiovascular Malformations
<28	2086 (0.4)	13 (0.62; 0.37–1.06)
28–31	4695 (0.9)	60 (1.28; 0.99–1.64)
32–36	31 297 (6.0)	401 (1.28; 1.16–1.41)
≥37	483 541 (92.7)	2490 (0.51; 0.50–0.54)
Total	521 619 (100)	2964 (0.57; 0.55–0.59)

were present at 12.8 cases per 1000 infants born at 32 to 36 weeks of gestation, 12.8 cases per 1000 infants born at 28 to 31 weeks of gestation, and 6.2 cases per 1000 infants born at <28 weeks of gestation (Table 1). There was no strong evidence of a real difference between these groups because of the small number of infants born at <28 weeks of gestation.

Preterm Births Among Infants With Cardiovascular Malformations

Using published data, we assumed that 7.3% of all infants are born at <37 weeks of gestation (Fig 1). We found that 474 infants (16%) with cardiovascular malformations were born before 37 weeks of gestation, giving an OR for prematurity among infants with cardiovascular malformations of 2.4 (95% CI: 2.2–2.7). More infants were born preterm with diagnoses of pulmonary atresia with ventricular septal defect (23%), complete atrioventricular septal defect (22%), and coarctation of the aorta, tetralogy of Fallot, and pulmonary valve stenosis (each 20%) (Table 2 and Fig 2). Fewer were born preterm with diagnoses of pulmonary atresia and intact ventricular septum (7%), transposition of the great arteries (8%), and single ventricle (9%). Statistical analysis showed

TABLE 2. Numbers of Preterm Infants and Total Live Births for Individual Cardiovascular Malformations

Diagnosis	No. Preterm	No. Total	Proportion Preterm, %	95% CI, %
PA/VSD	13	57	23	14–35
CAVSD	33	150	22	16–29
CoA	29	144	20	14–27
ToF	34	174	20	14–26
PS	48	237	20	16–26
VSD	228	1538	15	13–17
AS	15	100	15	9–23
TAPVC	7	46	15	8–28
CAT	6	46	13	6–26
HLH	7	66	11	5–20
SV	6	68	9	4–18
TGA	13	162	8	5–13
PA/IVS	2	27	7	2–23
Total CVMs	474	2964	16	15–17
No CVM	37 861	518 655	7.3	7.2–7.4

PA/VSD indicates pulmonary atresia with ventricular septal defect; CAVSD, complete atrioventricular septal defect; CoA, coarctation of the aorta; ToF, tetralogy of Fallot; PS, pulmonary valve stenosis; VSD, ventricular septal defect; AS, aortic valve stenosis; TAPVC, total anomalous pulmonary venous connection; CAT, common arterial trunk; HLH, hypoplastic left heart; SV, single ventricle; TGA, transposition of the great arteries; PA/IVS, pulmonary atresia with intact ventricular septum; CVM, cardiovascular malformation.

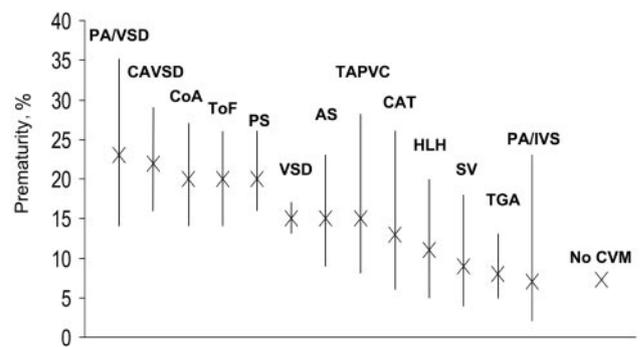


Fig 2. Prevalence of premature births among infants with specific cardiovascular malformations, ranked according to the prevalence of prematurity, and among infants without cardiovascular malformations. Vertical bars indicate 95% CIs. PA/VSD indicates pulmonary atresia with ventricular septal defect; CAVSD, complete atrioventricular septal defect; CoA, coarctation of the aorta; ToF, tetralogy of Fallot; PS, pulmonary valve stenosis; VSD, ventricular septal defect; AS, aortic valve stenosis; TAPVC, total anomalous pulmonary venous connection; CAT, common arterial trunk; HLH, hypoplastic left heart; SV, single ventricle; TGA, transposition of the great arteries; PA/IVS, pulmonary atresia with intact ventricular septum; CVM cardiovascular malformation.

that the differences between these diagnostic groups were significant ($\chi^2 = 28.0, P = .005$).

To investigate the possibility of an ascertainment bias toward increased detection of more minor malformations among preterm infants because of increased medical surveillance early in life, infants with ventricular septal defect were analyzed according to the need for surgery in the first 1 year. We found that 18% of infants in the surgical group were preterm, compared with 13% in the nonsurgical group. Preterm infants with ventricular septal defect required surgery in 30% of cases, compared with 23% of term infants with ventricular septal defect. These figures show that the excess of cardiovascular malformations among preterm infants cannot be explained by greater ascertainment of minor ventricular septal defects. Most of the other malformations considered (with the exception of some cases of aortic valve stenosis and pulmonary valve stenosis) are major and would have complete ascertainment in infancy regardless of gestational age. The median age at diagnosis for preterm infants was 19 days (interquartile range: 4–59 days), and that for term infants was 12 days (interquartile range: 4–74 days).

Other Influences

The strong associations between complete atrioventricular septal defect and trisomy 21 and between pulmonary atresia with ventricular septal defect and 22q11 deletion are well recognized. To investigate the possible contribution of chromosomal abnormalities to preterm birth in these groups, we analyzed the gestational age of all infants with trisomy 21 or with 22q11 deletion in the same population. In our 15-year study period, 646 live-born infants were recognized as having trisomy 21; gestational age data were available for 609. Of these, 149 (25%; 95% CI: 21–28%) were born preterm. Complete atrioventricular septal defect was diagnosed for 16% of preterm

infants with trisomy 21 and 16% of term infants with trisomy 21. Previously published work from this unit showed that approximately two thirds of infants with complete atrioventricular septal defect have trisomy 21.¹⁶ Therefore, the increase in preterm births among infants with trisomy 21 probably explains some of the excess of preterm births among infants with complete atrioventricular septal defect.

Only 4 of 38 infants (11%; 95% CI: 4–24%) with 22q11 deletion were born preterm. None of those infants had pulmonary atresia with ventricular septal defect; therefore, 22q11 deletion does not explain the excess of preterm births among infants with pulmonary atresia with ventricular septal defect.

To investigate the possible influence of prematurity of twins on our findings, we analyzed data from the Northern Multiple Pregnancy Register.¹⁷ Since 1998, this survey has collected prospective data on all multiple pregnancies for the same population as in our study. In 1998–2002, there were 4115 live-born twins, representing 2.7% of all live births. This is consistent with findings in published reports dealing with the same years.¹⁸ Most reports showed an increase in the incidence of live-born twins from ~2% in the 1980s to ~3% in the 1990s; therefore, a more accurate twin rate over the 15 years of our study might be 2.5%.¹⁸ In the Northern Multiple Pregnancy Register data, 46 of 4115 live-born twins were recognized as having a cardiovascular malformation in the first 1 year of life, a rate of 1.1 case per 1000 live births. In the same data, 52% of twin maternities (pregnancies resulting in ≥1 live birth or stillbirth) were delivered preterm. This finding is also consistent with reports in the literature showing that ~50% of twins are born before 37 weeks of gestation.¹⁹ In our study, 112 of 2964 infants with cardiovascular malformations were twins (3.8%) and 88 of these (79%) were born preterm. From these data, we can conclude that 18% of all preterm infants are twins, 1.3% of all term infants are twins, 23% of preterm infants with cardiovascular malformations are twins, and 1.3% of term infants with cardiovascular malformations are twins. Therefore, twins do not contribute significantly to the excess of cardiovascular malformations we observed among preterm infants.

Influence on Outcomes

The total 1-year mortality rate for infants of all gestational ages with cardiovascular malformations was 393 of 2964 infants (13%), and that for preterm infants with cardiovascular malformations was 97 of 494 infants (20%). Published studies of preterm infants, including our own population, predict that the overall 1-year mortality rate for preterm infants is 5.8%.^{10,11,14} In a comparison of our data for preterm infants with cardiovascular malformations with these population data, the OR for death in prematurity with cardiovascular malformations was 4.2 (95% CI: 3.1–5.5). Specific mortality rates for gestational age groups with and without cardiovascular malformations are shown in Fig 3. The mortality rate was higher at all gestational ages, but the effect was most marked for near-term (OR: 11.0) and term (OR: 35.6) infants.

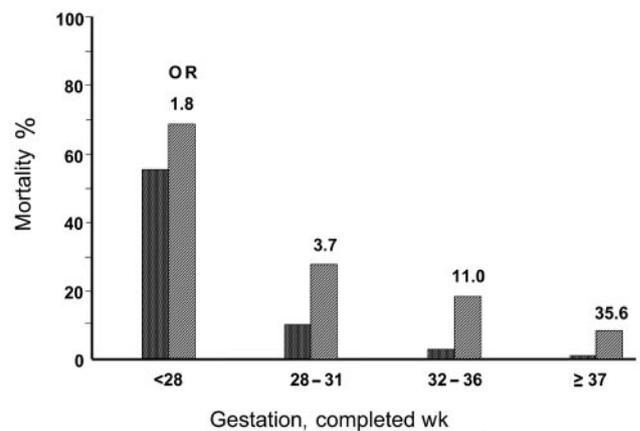


Fig 3. Total infant (12-month) mortality rates for different gestational age groups. Dark bars indicate infants without cardiovascular malformations; light bars, infants with cardiovascular malformations. ORs are for excess deaths among infants with cardiovascular malformations in each gestational age group.

DISCUSSION

This study showed that preterm infants have more than twice as many cardiovascular malformations as do infants born at term and that 1 of 6 infants with cardiovascular malformations is born preterm. It also showed, not surprisingly, that there is an increased mortality rate for infants born both preterm and with a cardiovascular malformation. The additional effect of cardiovascular malformations on mortality rates is most marked for term and near-term infants, for whom mortality rates are otherwise low. All mortality rates quoted in this study are from all causes in the first 1 year of life, not necessarily as a result of the cardiovascular malformation. We were not able to determine retrospectively the contribution of the cardiovascular malformations to the deaths. In a previous study of infants with esophageal atresia, we showed a sevenfold increase in mortality rates for those who also had a cardiovascular malformation but the heart defect was mainly a marker of multiple abnormalities and other syndromes, rather than being the cause of death.²⁰

Infants with some malformations (notably pulmonary atresia with ventricular septal defect and complete atrioventricular septal defect) had a higher prevalence of prematurity; for those with other malformations (such as transposition of the great arteries), preterm birth was less common, and the differences were statistically significant (Fig 2). The association between trisomy 21 and prematurity shown in this study goes some way to explain the excess rate of prematurity in complete atrioventricular septal defect, but the larger number of preterm births in pulmonary atresia with ventricular septal defect is not explained by the association with 22q11 deletion. The associations between other chromosomal abnormalities or syndromes and specific cardiovascular malformations are less common, which precludes detailed analysis.

One obvious limitation of our study is that we have no local population data on gestational ages or mortality rates according to gestational age. No such data are collected nationally in the United King-

dom.²¹ We therefore used 6 published reports from matching time periods and from populations with similar ethnic distributions (using non-Hispanic white infants from US studies¹³) to derive the proportions of infants born at various gestational ages and the mortality rates according to gestational age. The very close agreement between these studies shown in Fig 1 gives us confidence in using our assumed proportions of infants born in each gestational age group.

There has been no previous comparable population-based study with ascertainment of cardiovascular malformations among both preterm and term infants. In a small study from a single neonatal unit, Kecskes and Cartwright²² reported a prevalence at live birth of cardiovascular malformations of 23 cases per 1000 infants of <1500 g born at gestational ages of 24 to 36 weeks. Those authors found the most common abnormalities to be ventricular septal defect and coarctation, a finding not confirmed in our study. Their study had no denominator group of term infants, no ascertainment of diagnoses made after initial discharge from the hospital, and no correction for ascertainment bias related to referral patterns. Dees et al,²³ in a larger study of admissions to a single NICU, found 16 per 1000 infants had cardiovascular malformations. There was no denominator of term infants and no population data, but those authors did report an increased prevalence of "conotruncal defects," compared with the Baltimore-Washington Infant Study²⁴ (which itself had a fairly low overall ascertainment rate). Dees et al²³ found that the in-hospital mortality rate for preterm infants was increased by a factor of 2.6 by the presence of a cardiovascular malformation and the risk of necrotizing enterocolitis was increased by a factor of 1.7. The mortality rate for cardiac surgery was twice as high among preterm infants, compared with term infants. We also found an increase in the mortality rate for preterm infants with cardiovascular malformations, but we did not investigate the relative contributions of different causes of death. Reddy,²⁵ in a report on cardiac surgery among infants of <2500 g, noted a significant increase in the mortality rate, compared with larger infants undergoing similar surgical repair. However, 2 recent European retrospective reports of cardiac surgery among neonates weighing <2500 g found that, although nearly one half were preterm, this was not an additional risk factor for early death.^{26,27} Jenkins et al²⁸ used data sets from the Pediatric Cardiac Care Consortium and hospital discharge data from Illinois, Massachusetts, and California to develop and to validate a risk adjustment score for surgery to treat congenital heart disease. The prevalence rates of codes for prematurity in the 2 data sets were 7.8% and 1.7%, respectively. Prematurity was an additional predictor of risk (after type of operation, age at operation, and presence of major noncardiac malformation), with ORs for in-hospital death of 1.8 (95% CI: 1.3–2.6) and 2.9 (95% CI: 1.5–6.0), respectively, in the 2 data sets. McElhinney et al,²⁹ in a study of neonatal admissions to a cardiac ICU, found that prematurity was asso-

ciated with an OR of 3.9 for development of necrotizing enterocolitis.

We analyzed the data in this study according to anatomic diagnosis. Several methods have been proposed to group anatomic diagnoses into speculative etiologic groups. They include a "mechanistic classification"²⁴ and a "potential morphogenetic classification."³⁰ There are similarities but also inconsistencies between these classifications, and they group together malformations that may be unrelated embryologically, etiologically, or physiologically; therefore, we did not apply such an analysis to our data.

There has been interest in the relationship between birth weight and prevalence at live birth of cardiovascular malformations, and there is an obvious relationship between birth weight and gestational age.²¹ Although birth weight was recorded for all cases in our register, our analysis was on the basis of gestational age alone. Rosenthal et al³¹ reported a case-control study of birth weight in relation to estimated gestational age among singleton infants with a limited range of isolated cardiovascular malformations. They found a significant increase in the likelihood of being small for gestational age among infants with tetralogy of Fallot, complete atrioventricular septal defect, hypoplastic left heart, or large ventricular septal defect. Their data also showed an increased prevalence of prematurity among infants with tetralogy of Fallot, pulmonary stenosis, aortic stenosis, coarctation of the aorta, or ventricular septal defect. Kramer et al³² reported birth weights for 842 infants with cardiovascular malformations. They also found an increase in the chance of being small for gestational age among infants with tetralogy of Fallot, complete atrioventricular septal defect, or pulmonary stenosis. A larger proportion of infants with pulmonary stenosis and complete atrioventricular septal defect were premature, although the differences were not significant.

In common with most centers, we have an increasing number of infants born live after prenatal diagnosis of a cardiovascular malformation. It is unlikely that this has any significant influence on gestational age at delivery, because our policy is not to recommend premature delivery. Published evidence does not suggest that infants with prenatal diagnoses of cardiovascular malformations are born significantly earlier than those without.³³

The excess of cardiovascular malformations among preterm infants shown in this study is intriguing but not easy to explain. Hoffman,³⁴ in a review of cardiovascular malformations in prenatal life, reported a much increased prevalence among late stillbirths. Early fetal losses are often associated with chromosomal abnormalities, many of which involve cardiovascular malformations, but chromosomal abnormalities are much less common after 20 weeks of gestation. The review by Hoffman³⁴ states that it is difficult to give an accurate estimate of the frequency of cardiovascular malformations, because of the disparate nature of reports available, but there are major differences in the number and spectrum of cardiovascular malformations, compared with those seen in postnatal life. In particular, there are higher

incidence rates of coarctation of the aorta, double-inlet left ventricle, hypoplastic left heart, truncus arteriosus, double-outlet right ventricle (a diagnostic category we did not use), and atrioventricular septal defect among stillbirths. Interestingly, this spectrum of malformations is similar to that shown in Fig 2 and those reported by Rosenthal et al³¹ and Kramer et al,³² as discussed above. Whether the increased prevalence of cardiovascular malformations among preterm infants and the increase in stillbirths reported by Hoffman³⁴ suggest clues to the cause is difficult to say. In many cases, it is not clear that the cardiovascular malformation led to preterm birth or stillbirth; we know that most cardiovascular malformations have little effect on the developing fetus and become hemodynamically significant only after birth.^{35,36} There is also no evidence that cardiovascular malformations are associated with any compromise of placental function that might precipitate preterm delivery or cause stillbirth.

ACKNOWLEDGMENTS

We are indebted to the Children's Heart Unit Fund for financial support for the pediatric cardiology database, to Valerie Sutherland for help with data collection, to the Northern Congenital Abnormality Survey for additional data, and to Professor John Matthews for statistical advice.

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DOI: 10.1542/peds.2005-0397

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