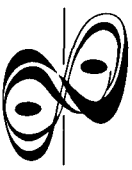

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# Congenital Anomalies in Twins in Northern Ireland III: Anomalies of the Cardiovascular System, 1974-1978

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**Abstract.** Rates of congenital anomalies of the cardiovascular system were compared between twins and singletons in a population-based study in Northern Ireland during the period 1974-1978. Multiple sources of ascertainment were used. As in previous studies, the rate of anomalies of the cardiovascular system in twins (91.0/10,000) was higher than the rate in singletons (66.4/10,000). The excess was confined to twins from pairs of like sex and, in the main, anomalies of the circulatory system other than of the heart itself were involved. Problems in the interpretation of this excess are discussed. No twins were concordant for congenital cardiovascular anomalies of any type.

**Key words: Congenital anomalies, Cardiovascular disease, Twinning, Ascertainment**

## INTRODUCTION

Anomalies of the cardiovascular system are among the most frequent types of congenital anomaly and pose a significant public health problem. In pooled data from a number of centres in Europe during the period 1980-1983, for example, 22% of malformed babies had an anomaly of the heart or great vessels [21]. As congenital anomalies become relatively more important in the list of potential problems encountered by twins[4], reports [4,8,18,19,22,24] of an excess of such anomalies in twins become of increasing importance. In many previous studies, it has been difficult to conclude that the excess is real [4,14,] because: 1) data are available only for the perinatal period, giving rise to problems of ascertainment and diagnostic confirmation; and 2) the contribution of certain perinatal cardiac complication

eg, cardiac enlargement in the recipient of feto-fetal transfusion syndrome, patent ductus arteriosus in preterm infants to the excess has not been clarified.

In this paper, the results are presented of a large population-based survey in Northern Ireland, in which multiple sources of ascertainment were used.

## METHODS

As described elsewhere [16], the denominator data on births were obtained from the Child Health System. Individual birth records coded as twins were linked in pairs by computerised comparison of a series of variables; doubtful matches were checked against the original Child Health records. During the period 1974-1978, 127,959 live births were identified as singleton, 2,636 as twin, 45 as triplet, 13 as multiple with no further details, and 228 as of unknown multiplicity.

Data on births with anomalies of the cardiovascular system were obtained from seven sources:

1) the Child Health System (CHS), based on statutory notification of birth and mandatory follow-up by the Health Visitor, after birth in the case of domiciliary confinements, and after discharge in the case of hospital confinements;

2) the Registrar General's Congenital Malformation Notification (RG), a voluntary system whereby doctors or other Community Health Staff notify babies with congenital anomalies encountered in their practice in a period between four and eight weeks after birth;

3) records of three major maternity and neonatal units, into which substantial numbers of infants with problems manifest in the perinatal period are transferred from other units;

4) pediatric case indices which covered the work of consultants in the province to whom children with cardiovascular problems are referred, and included records of all investigations performed on an in- or outpatient basis, and of all relevant surgical procedures;

5) records of the Regional Genetics Centre which is responsible for all the counselling clinics and for the cytogenetics laboratory in the province;

6) autopsy records;

7) death certificates.

Discrepancies in diagnosis between sources can arise when multiple sources of ascertainment are used. A hierachy of sources of information was established (Figure) and the final diagnosis was agreed with a pediatrician or a medical geneticist.

For congenital heart disease in general, the diagnoses considered were selected from the Eighth Revision of the International Classification of Diseases [25]: congenital anomalies of the heart and circulatory system (codes 7460-7479), situs inversus (7590), disease of the cardiovascular system other than rheumatic heart fever, hypertensive disease and other acute heart disease (4230-4589) – and its supplements [3,9] – neonatal cardiac failure (7824,778902), innocent murmurs (79381, 79391), transient murmurs (778916), and murmurs not otherwise specified (778907). Analysis relating to specific anomalies and groups of anomalies was restricted to the range of codes 7460-7479.

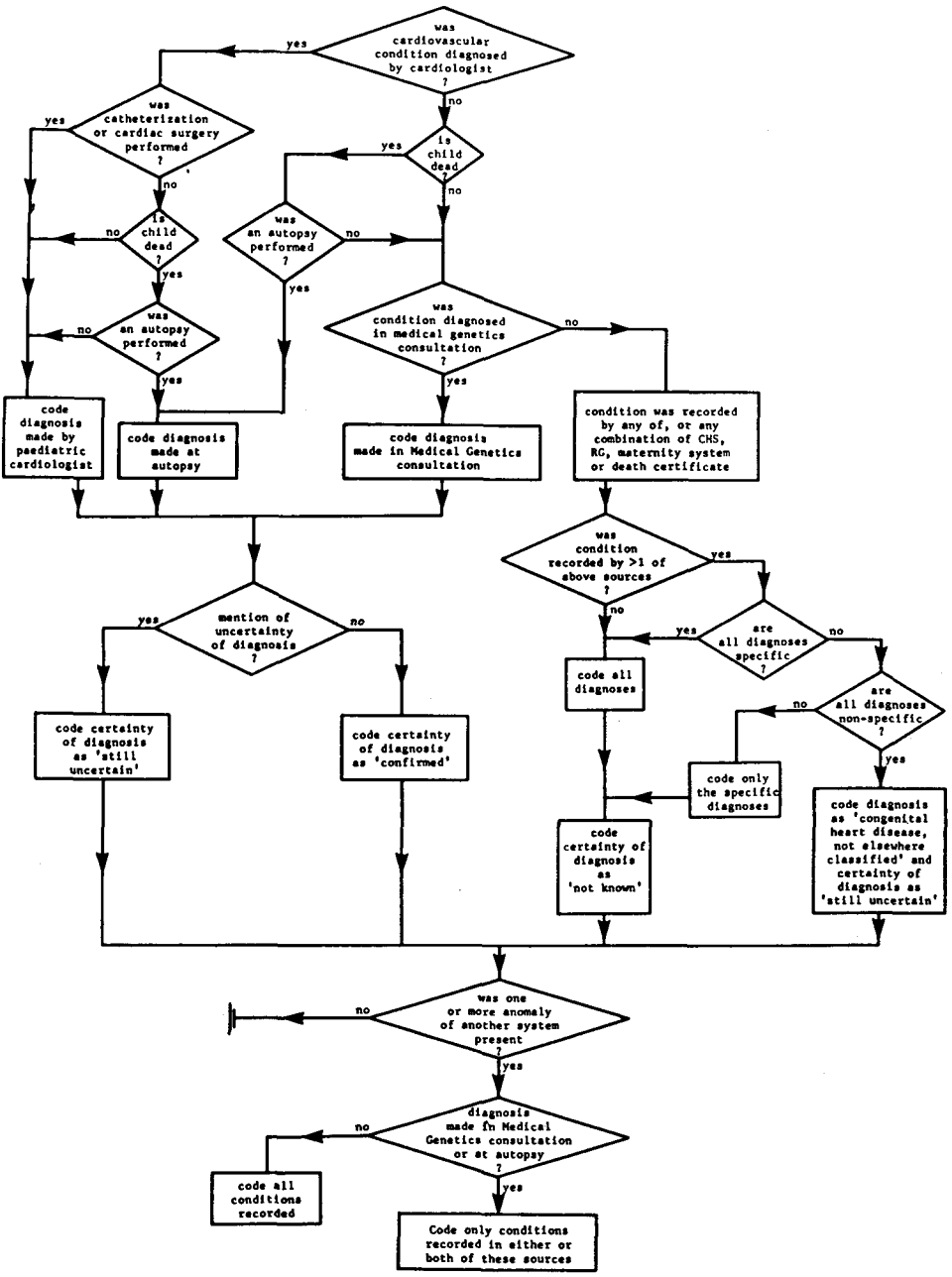


**Figure.** Summary of coding priorities for data on anomalies of the CVS from Northern Ireland.

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## RESULTS

Of 85 stillborn twins, none was reported as having a cardiovascular anomaly. All subsequent analysis, therefore, is confined to livebirths.

**Table 1 - Main sources of information about the diagnosis, by multiplicity: Northern Ireland, 1974-1978**

| Main source | Singletons | | Twins | |
|---|---|---|---|---|
| | N | % | N | % |
| Pediatric case indices | 441 | 48.9 | 9 | 34.6 |
| Autopsy records | 133 | 14.8 | 2 | 7.7 |
| Regional Genetics Centre | 11 | 1.2 | 0 | 0.0 |
| CHS, RG, maternity system or death certificate: | | | | |
| > 1 of these | 149 | 16.5 | 5 | 19.2 |
| 1 only of these | 163 | 18.1 | 10 | 38.5 |

**Table 2 - Anomalies of the cardiovascular system in livebirths in singletons and twins, by sex type of pair: Northern Ireland, 1974-1978**

| Type of anomaly | Singletons | | RR | Twins | | | | | | RR |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Total | | Like sex | | Unlike sex | | |
| | N | Rate per 10,000 | T:S | N | Rate per 10,000 | N | Rate per 10,000 | N | Rate per 10,000 | L:U |
| Bulbus cordis anom. & anom. of cardiac septal closure | 477 | 37.3 | 1.0 | 10 | 37.9 | 7 | 39.4 | 3 | 34.9 | 1.1 |
| Other anomalies of heart | 295 | 23.1 | 1.2 | 7 | 26.6 | 5 | 28.2 | 2 | 23.3 | 1.2 |
| Other anomalies of circulatory system | 313 | 24.5 | 1.5 | 10 | 37.9 | 8 | 45.0 | 2 | 23.3 | 1.9 |
| Subtotal | 850 | 66.4 | 1.4 | 24 | 91.0 | 18 | 101.4 | 6 | 69.8 | 1.5 |
| All congenital heart disease | 901 | 70.4 | 1.4 | 26 | 98.6 | 18 | 101.4 | 6 | 69.8 | 1.5 |
| Total livebirths | 127,959 | | | 2,636[a] | | 1,776 | | 860 | | |

RR, T:S = Ratio of rate of anomalies in twins to that in singletons.
RR, L:U = Ratio of rate of anomalies in twins of like sex to that of twins of unlike sex.
[a] Of these, 58 were from pairs of unknown sex type.

The main sources of information about the diagnosis are summarized in Table 1. The proportion (42%) of twins for whom the main source of diagnostic information was a pediatric case index, an autopsy record or a record in the Regional Genetics Centre was smaller than that of singletons (65%).

Similarly, the proportion of twins subjected to catheterization or surgery (56%) was smaller than that of singletons (66%). In consequence, the proportion of twins whose diagnosis was confirmed as certain (35%, ie, 9 of 26) was also less than that of singletons (60%, ie, 539 of 901).

Overall, there is a modest excess of cardiovascular anomalies in twins (Table 2). This is largely accounted for by anomalies classifiable to the ICD category "other anomalies of the circulatory system" [25] and is confined to twins from pairs of like sex. Table 3 illustrates the difficulty of making comparisons for specific anomalies.

Analysis of the effect of sociodemographic factors on the associations between twinning and congenital heart disease of all types shows that there was an excess risk to twins born in the Eastern and Northern areas of the province and also to twins who were delivered to young (< 35 years) mothers. In addition, rates of anomalies were high in 1974, 1977 and 1978 and in *female* (16 cases out of 24) twins. However, patterns of association are difficult to interpret because of the small number of cases.

First-born (N = 11) and second-born (N = 13) twins appeared equally likely to be affected.

No twins were concordant for congenital cardiovascular anomalies of any type.

**Table 3 - Specific anomalies of the cardiovascular system in livebirths between singletons and twins: Northern Ireland, 1974-1978.**

| Type of anomaly | Singletons | | RR | Twins | |
|---|---|---|---|---|---|
| | N (n multiple cardiac) | Rate per 10,000 | T:S | N (n multiple cardiac) | Rate per 10,000 |
| Common truncus | 23 (19) | 1.8 | 2.1 | 1 (0) | 3.8 |
| Transposition of great vessels | 56 (42) | 4.4 | 0.9 | 1 (0) | 3.8 |
| Ventricular septal defect | 308 (149) | 24.1 | 0.8 | 5 (2) | 19.0 |
| Atrial septal defect | 162 (121) | 12.7 | 0.6 | 2 (2) | 7.6 |
| Unspecified defect of septal closure | 3 (0) | 0.2 | 38.0 | 2 (0) | 7.6 |
| Tricuspid valve insufficiency | 4 (4) | 0.3 | 12.7 | 1 (1) | 3.8 |
| Right bundle branch block | 3 (1) | 0.2 | 19.0 | 1 (0) | 3.8 |
| Heart block | 3 (1) | 0.2 | 19.0 | 1 (1) | 3.8 |
| Patent ductus arteriosus | 195 (101) | 15.2 | 1.0 | 4 (0) | 15.2 |
| Coarctation of the aorta | 56 (38) | 4.4 | 1.7 | 2 (0) | 7.6 |
| Interrupted aortic arch | 7 (7) | 0.5 | 7.6 | 1 (1) | 3.8 |
| Single umbilical artery | 17 (0) | 1.3 | 5.8 | 2 (0) | 7.6 |
| Other anomaly of peripheral arteries | 6 (6) | 0.5 | 7.6 | 1 (1) | 3.8 |
| Persistent left superior vena cava | 10 (10) | 0.8 | 4.8 | 1 (1) | 3.8 |
| Multiple cardiac | 254 | 19.9 | 0.6 | 3 | 11.4 |

RR, T:S = Ratio of rate of anomalies in twins to that in singletons.

**Table 4 - Pregnancy outcome status associated with some specific anomalies of the cardiovascular system: Northern Ireland, 1974-1978**

| Anomalies | Outcome status (rates per 10,000 livebirths) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Twins | | Singletons | | | | | |
| | N | Rate | Low birthweight | | Long gestation | | Term | |
| | | | N | Rate | N | Rate | N | Rate |
| Patent ductus arteriosus | 4 | 15.2 | 39 | 65.3 | 6 | 17.1 | 119 | 10.6 |
| Single umbilical artery | 2 | 7.6 | 8 | 13.4 | 0 | 0.0 | 8 | 0.7 |
| Murmurs | 1 | 3.8 | 4 | 6.7 | 0 | 0.0 | 21 | 1.9 |
| Arrhythmias | 0 | 0.0 | 3 | 5.0 | 1 | 2.9 | 3 | 0.3 |
| Congenital heart disease, not further specified | 5 | 19.0 | 36 | 60.3 | 1 | 2.9 | 79 | 7.0 |
| Total livebirths | 2,636 | | 5,974 | | 3,504 | | 112,404 | |

## DISCUSSION

The present study is one of the largest relating to the association between congenital cardiovascular anomalies and twinning in which multiple sources of ascertainment have been used [13]. The use of multiple sources does not exclude the possibility that delivery of twins may prompt more intensive examination for anomalies than delivery of singletons [14]. Elsewhere, we have considered this possibility for "minor" anomalies of other systems [16]. Any excess of "minor" malformations was least marked for twins. In Table 4, rates of patent ductus arteriosus, single umbilical artery, cardiac murmurs, arrhythmias and congenital heart disease of unspecified type are compared between liveborn singletons of low birthweight, liveborn singletons of long gestation and liveborn singleton term infants. As expected, rates of patent ductus arteriosus were highest in infants of low birthweight, and were higher in twins than in singleton term infants but, surprisingly, lower than in singletons of long gestation. Rates of single umbilical artery, of murmurs, and of unspecified congenital heart disease were higher in twins and in infants of low birthweight than in infants from the other categories. The excess was more marked for infants of low birthweight. The relatively high rates of these anomalies in twins suggest that anomalies of the cardiovascular system either of insufficient severity to require investigation in later life, or which are not confirmed on follow-up, are more likely to be recorded in twins than in singletons in the perinatal period. This observation is consistent with the fact that the proportion of twins with anomalies of the cardiovascular system recorded in pediatric case indices, autopsy records or records of the Regional Genetics Centre was lower than that of singletons (Table 1). Single umbilical artery accounts for some, but not all, of the excess risk in twins of

"other anomalies of the circulatory system" (Tables 2 and 3). However, if there had been substantial bias of ascertainment, it is surprising that no twins were found to be concordant for congenital cardiovascular anomalies of any type. Moreover, the excesses are less marked than for infants of low birthweight, so are more likely to be attributable to the association between twinning and prematurity. Three of the twin infants with patent ductus arteriosus were delivered preterm, the other being of unknown gestation, and all of the twin infants with unspecified congenital heart disease were delivered preterm. It may be postulated that, in this population, a premature infant with a patent ductus is equally likely to be classified as having unspecified congenital heart disease as having the specific anomaly itself.

The finding of a moderate excess in twins is consistent with previous reports, even though these vary widely in method of confirming diagnosis [5,13].

When comparison is made between the rates estimated in the present study and those estimated from the three largest published studies with follow-up beyond the perinatal period [4,11,18,19], the results are inconsistent. Much of the excess in the NCPP study [18,19,20] is attributable to cardiac enlargement, a nonspecific diagnosis. Furthermore, this is the only study in which an excess risk of atrial septal defect is recorded, probably a result of repeated physical examination up to the age of seven.

The overall rates of cardiovascular anomalies estimated from data for the period 1974-1979 from the perinatal sources (CHS & RG) in the present study, and the ratios of the rate in twins to that in singletons, are very similar to the figures estimated from neonatal data for Norway [24].

Few data are available on specific anomalies. An excess risk of ventricular septal defect has been reported in Metropolitan Atlanta [12] and in the NCPP study [20] but was not found in the present study. Only in Metropolitan Atlanta has an increased frequency of patent ductus arteriosus been demonstrated [12]; it is not clear to what extent this excess is due to the increased incidence of premature delivery of twin maternities. Comparison of other specific cardiovascular anomalies is difficult because of their rarity, and the varying study methods would make pooled data difficult to interpret. In a number of studies of the prevalence of twins in series of infants with specific types of congenital heart anomalies, the twinning rate has been similar to the widely quoted figure of 2% for the general population [1,7].

The finding that any excess of congenital cardiovascular anomalies is confined to twins from pairs of like sex is consistent with the almost universal finding in surveys of case-series of a high ratio of twins from pairs of like sex to twins from pairs of unlike sex [15]. However, the results of prevalence surveys have not been consistent. An excess in pairs of like sex [8,12,17], and also in MZ pairs [4,6,11], has been found by some but not by others [5,24].

We found an even more pronounced female excess (male preportion in twins = 0.33 vs 0.52 in singletons) than has been reported from Sweden [10]. Also as noted in the Swedish study [10], we found no effect of the birth order of twins.

Finally, the finding that no pairs were concordant for congenital heart disease is consistent with low concordance rates reported in literature [2,4,6,12,18,23].

## CONCLUSION

As found in previous studies, there was an excess of anomalies of the cardiovascular system in twins. The rate of patent ductus arteriosus was similar in singletons and twins, so the overall excess in the present study cannot be attributed to the association between twinning and prematurity. The excess of single umbilical artery and of unspecified congenital heart disease might be taken as suggestive of some bias of ascertainment, but are less marked than for low birthweight, so the association between twinning and prematurity is a more likely explanation. Therefore, we concluded that some of the excess is real, involving, in the main, anomalies of the circulatory system other than the heart itself. The excess was confined to pairs of like sex, in line with data from case series.

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