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Congenital Anomalies in Twins in Northern Ireland II: Neural Tube Defects, 1974-1979

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Abstract. In a large population-based study in Northern Ireland during the period 1974-1979, the rate of anencephalus in twins (9.1/10,000) was found to be less than that in singletons (24.3/10,000). This finding is in contrast with most other studies and the possibility of underascertainment of twin cases is considered, but it is concluded that chance is the likeliest explanation. The rate of spina bifida in twins (36.4/10,000) was similar to that in singletons (31.9/10,000). All of the twins with anencephalus were female and from pairs of like sex. Rates of spina bifida in twins from pairs of the two sex types were similar but, unusually, there was a male preponderance. As in previous studies, the great majority of twins with NTDs had unaffected cotwins.

Key words: Twins, Ascertainment, Discordance, Neural tube defects, Anencephalus, Spina bifida, Encephalocele

INTRODUCTION

The association between twinning and neural tube defects (NTDs) is of importance for two reasons. Firstly, as only one infant usually is affected in a recognised twin pregnancy, there is a need for counselling whether the affected pregnancy is terminated or the affected baby is stillborn or dies soon after birth or the affected infant survives. There are also problems of bringing up children of the same age with different physical, and perhaps mental, needs. Secondly, the association may provide clues as to the etiology of NTDs. Several reports have suggested a common etiology for NTDs and certain types of twinning [6,8,17,19,20,38], which would result in a positive association. It also has been suggested that NTDs arise from

interaction between twin conceptuses. The proposed mechanisms which include fusion of embryos [24,36,37], and the vascular consequences of fetal death [27], would be expected to give rise to a negative association between NTDs and twinning as the twins would either be absorbed into the cotwin or might not be recognised at birth.

The pattern of association between NTDs and twinning is unclear. In a comprehensive review, in pooled data on cases of NTD, the total number of twins was slightly lower than that expected on the basis of twinning rates in the same populations [8]. There was, however, considerable fluctuation in the individual series from which the data had been pooled. It has been suggested that an excess of twins among NTD cases is to be expected only in areas of low risk as a result of increased susceptibility of twin embryos and fetuses to environment insults; in areas of high risk the inferred increased total population exposure to environment risk factors would obscure any positive association with twinning [44]. Review of the studies [Table 11.5 of 27, and 1,12,13,14, 21,23,35,39] in which the populations at risk has been enumerated, directly or indirectly, and the total numbers of twins and singletons with NTDs are known, suggests that there is a moderate excess (ratio of rate in twins to rate in singletons = 1.2) of anencephalus in twins in the high risk populations of the British Isles, and that there is an excess of similar magnitude in other populations. Analysis of pooled data on spina bifida shows a small deficit in twins. Within the British Isles, the most pronounced excesses of anencephalus are in the low risk areas of Oxford [9] and Southampton [43], but this pattern is not clearly apparent in other areas or for spina bifida. Thus, there is a need for further clarification. As most of the available studies relate to the 1960's and early 1970's, this is important in view of the declining rates of NTDs.

The highest rate of NTDs in a population-based study reported in the literature is for Northern Ireland in the 1960s [5]. The present paper relates to a large-scale population-based study in Northern Ireland in the late 1970s, and adds to the literature on the association between twinning and NTDs in an area of high risk.

METHODS

As already described [29], data on the denominator population for the period 1974-1979 were obtained from the Child Health System. Individual birth records coded as twins were linked in pairs by comparison of a series of variables. Where linkage was uncertain, confirmation was sought from the appropriate administrative authority (Health and Social Services Board) in the area in which the birth took place. A total of 157,068 births were identified as singletons and 3,294 as twins.

Data on births with NTDs were obtained from two sources. Firstly, the Child Health System includes data from the notification of birth (live or still) required by the law within 36 hours of delivery, and the first mandatory follow-up visit by the Health Visitor, after birth in the case of domiciliary confinements, after dis-

Table 1 - Comparison of prevalence at birth of specific NTDs between twins of different types and singletons: Northern Ireland, 1974-1979

Anomaly	Twins							Singletons		RR	
	Like sex		RR	Unlike sex		Total		N (n stillborn)	Rate per 10,000	T:S	L:S
	N (n stillborn)	Rate per 10,000	L:U	N (n stillborn)	Rate per 10,000	N (n stillborn)	Rate per 10,000				
Anencephalus	3 (3)	13.5	∞	0 (0)	0.0	3 (3)	9.1	381 (288)	24.3	0.4	0.6
Spina bifida +/- hydrocephalus[1]	8 (1)	36.0	1.0	4 (0)	37.4	12 (1)	36.4	501 (72)	31.9	1.1	1.1
Encephalocele	1 (0)	4.5	∞	0 (0)	0.0	1 (0)	3.0	55 (15)	3.5	0.9	1.3
All NTDs	12 (4)	54.0	1.4	4 (0)	37.4	16 (4)	48.6	918 (366)	58.4	0.8	0.9

[1] Excludes cases with anencephalus (73 cases, 53 of which stillborn; all singletons).

RR, L:U = Ratio of rate of anomaly in twins of like sex to that in twins of unlike sex.

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

RR, L:S = Ratio of rate of anomaly in twins of like sex to that in singletons.

charge in the case of hospital confinements. Secondly, the Registrar General's Congenital Malformation Notification is a voluntary system whereby doctors or other Community Health Staff notify births with congenital anomalies encountered in the course of their practice. Notification is intended to be made in a period between four and eight weeks after birth, so that the individual making the notification can confirm the diagnosis. However, the information is recorded for all stillbirths of 28 weeks or more gestation, livebirths, and early deaths, irrespective of gestational age [33].

RESULTS

Overall, there was a slight deficit of NTDs among twins (Table 1). The reduced frequency of NTDs amongst twins is largely accounted for by anencephalus; the prevalence rates at birth of spina bifida and encephalocele in twins and singletons are similar.

The risk of NTDs was higher in twins of like sex than of unlike sex. All four cases of NTD in twins of unlike sex had spina bifida. The rate of anencephalus in twins of like sex was lower than the rate in singletons (Table 1).

One twin pair of like sex was concordant for spina bifida. Therefore, in these data, the overall concordance rate for spina bifida was 9.1% and for pairs of like sex 16.7%. In one instance, a female twin with isolated spina bifida had a male cotwin with congenital dislocation of the hip.

The sex distribution for specific NTDs is shown in Table 2. All of the twins with anencephalus or encephalocele were female, whereas the majority of those with spina bifida were male. The difference in the male proportion between twins and singletons for NTDs of all types is not statistically significant ($\chi^2_{(1)} = 3.69$).

Female births with NTDs were substantially more likely to be stillborn than males (Table 3). The pattern was particularly marked for twins of like sex, and is substantially more pronounced than in the general population.

Table 2 - Sex distribution of NTDs in twins and singletons: Northern Ireland, 1974-1979

	Twins			Singletons		
	Male	Female	Male proportion	Male	Female	Male proportion
Anencephalus	0	3	0.00	115	266	0.30
Spina bifida	10	2	0.83	231	269	0.46
Encephalocele	0	1	0.00	16	39	0.29
Total NTDs	10	6	0.63	348	548	0.39
Population	1,651	1,643	0.50	80,946	76,572	0.51

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Table 3 - Proportion of stillbirths among male and femele births, by multiplicity of birth

Multiplicity of birth	Male		Female	
	N	Stillborn (%)	N	Stillborn (%)
1. NTDs				
Twin:				
Like sex	7	0.0	5	80.0
Unlike sex	3	0.0	1	0.0
Total	10	0.0	6	66.7
Singleton	348	29.9	548	46.2
2. All births				
Twin				
Like sex	1,116	3.7	1,108	4.0
Unlike sex	535	1.5	535	1.5
Total	1,651	3.0	1,643	3.2
Singleton	80,496	1.0	76,572	1.1

DISCUSSION

In contrast to most previous reports, the rate of anencephalus in twins in Northern Ireland is less than that in singletons. In a previous study in Belfast, a lower frequency had also been found, but the magnitude of the deficit was much smaller [5]. The study in Belfast was based on more sources of ascertainment than in the present study, including in addition to a birth register and the voluntary notification system, hospitals in the Belfast area dealing with pediatric cases, medical genetics and cytogenetics records, death certificates and autopsy records. The rates in singletons both of anencephalus and of spina bifida are lower in the present study than in the previous study in Belfast, but this is consistent with other evidence of a decline in the rate of neural tube defects in the British Isles [2,10,25,30,32,34,35,42]. During the period 1974-1976, of 245 cases of anencephalus ascertained from the two sources on which the present study was based, genetic counselling clinics and autopsy records, some 218 (89%) were identified from the two sources employed in the present study [33]. Similar types of analysis could be carried out for the period 1974-1979. Firstly, for births in three major maternity units in Belfast, together accounting for about a quarter of births in the province, hospital records could be linked to the other two sources on which the present study was based. For singletons, these two sources identified 98% (89 of 91) of cases of anencephalus ascertained from all three sources. However, of two cases of anencephalus in twins, only one was identified by the two sources used in the present study. Secondly, for the whole province during the period 1977-1979, records of genetic counselling clinics could be considered. All cases of anencephalus in twins ascertained by the

three sources were recorded as such in the sources on which the present study was based; only 2 (out of 166) cases in singletons were missed. Moreover, in a study of factors influencing the relative probability of ascertainment of certain groups of specific anomalies in Belfast during the period 1974-1979, including neural tube defects, no association was found with multiplicity of birth [28]. It is unlikely that the deficit can be explained by prenatal diagnosis. In Northern Ireland, although mothers who have an infant with a neural tube defect have access to prenatal diagnosis, serum alpha-fetoprotein screening of antenatal patients is not routine [32]. In the period 1974-1979, 42 pregnancies were terminated on grounds of fetal neural tube defect, 2 of which were twin pregnancies in which the fetuses were concordant for spina bifida [32]. None of the fetuses with anencephalus was from a twin pregnancy. Moreover, selective abortion cannot be applied in the same way in twin and singleton pregnancies. These arguments do not exclude the possibility that after a normal livebirth with a stillborn cotwin, only the livebirth would be recorded. If this were so, then the rate of anomalies would be expected to be lower in stillbirths from twin maternities in which one twin was born alive and the other born dead, than in births from twin maternities in which both twins were stillborn. In the present study, there were 7 births (12.7%) with anomalies of any type in 55 stillbirths from twin maternities in which one twin was born alive and the other dead, as compared to 2 births (4.3%) in 46 stillbirths from twin maternities in which both twins were born dead. These rates are, however, substantially lower than the rate of anomalies in stillborns (28.0% – 476 out of 1698). Moreover, the proportion (25%) of twin babies with NTDs born dead is substantially lower than the corresponding figure of 40% for singletons (Table 1).

The methods of ascertainment in other studies in which a deficit of anencephalus in twins has been observed [4,5,11,14,31,35,39,41], have been varied. No clearcut pattern is apparent by period of study, criteria for including stillbirths or prevalence at birth in singletons. We therefore conclude that the deficit of anencephalus in twins in Northern Ireland is a chance finding.

No association between twinning and spina bifida was apparent in the present study. This is consistent with a number of previous reports from the British Isles [3,35,40] but not with the previous findings in Belfast of a deficit in twins [5]. As there were only about 1000 twin births in the Belfast study, chance is the likeliest explanation for the discrepancy. Again, small numbers of twin births may explain the absence of affected twin births in Southampton [43]. The association between twinning and spina bifida in areas other than the British Isles is inconsistent [27].

Within the population of twins, the three cases of anencephalus and the one case of encephalocele were all from pairs of like sex. This is consistent with James' conclusion that, on the basis of pooled data, the prevalence at birth of anencephalus is highest in twin pairs of like sex [17]. However, in the more recent review by Elwood and Elwood [8], in which studies which did not include stillbirths or for which there was other evidence of incomplete ascertainment were excluded, 279 of 385 (72%) twin pairs discordant or concordant for anencephalus and whose sex compostion was known were of like sex in contrast to an expected proportion of 67% to 69%. Reports which have been available more recently include the large study

from Japan [15] in which 56 (90%) of 62 affected pairs of known sex type were of the same sex. It would be inappropriate to pool the data from this study with data from other recent studies as opposite-sex twinning rates have been very low in Japan [18]. Addition of data from other recent reports [1,22,26,44 and present study] to the data of Elwood and Elwood [8] brings the total number of affected like-sex pairs to 308, 73% of the total (424) affected pairs of known sex type. In the periods when these studies were being carried out, opposite sex twinning rates declined [7,16,18], so the expected proportion of like sex would have increased. Interpretation of the evidence as to differences in rates by sex type (and, by inference, zygosity) is also complicated by the fact that in these pooled data on anencephalus, some 133 pairs were of unknown sex type. We therefore conclude that the available evidence does not indicate a difference in prevalence at birth of anencephalus by sex type.

The absence in the present study of a difference in rates of spina bifida between twins from pairs of like or unlike sex is also consistent with the findings of the review of Elwood and Elwood [8].

The observation of one like-sex pair concordant for spina bifida is not inconsistent with previous findings, based on pooled data, of a higher concordance rate for spina bifida than for anencephalus [8]. For both anomalies, concordance rates are higher for pairs of like sex than for pairs of unlike sex, but discordance is the norm.

The female preponderance in anencephalus, as was observed in the present study, is generally accepted [8]. The finding of a male preponderance in twins with spina bifida differs from other studies in which a modest female excess has been noted [8] but a male proportion as high as 0.67 has been found in pooled data from Norway and Los Angeles [44]. In Sweden, a male proportion of 0.90 for neural tube defects of all types has been observed in twins [23].

Like-sex twins were found more likely to be born dead than twins of unlike sex, especially if they were female. Females with NTDs, if singletons or twins from like sex pairs, were more likely to be stillborn than affected males. These observations on stillbirths of 28 weeks gestation or more are similar to those on pooled data from stillbirths of 16 weeks gestation or more in Norway and 20 weeks gestation or more in Los Angeles [44], except that no twins of unlike sex with NTDs were recorded as stillborn in the present study.

CONCLUSION

In contrast to previous studies, there was a marked deficit of anencephalus in twins. While bias of ascertainment cannot be excluded totally as a possible explanation, consideration of other sources of information for subsets of the population and comparison of methods between studies suggest that this is unlikely. The rates of spina bifida in twins and singletons were similar.

All of the twins with anencephalus were from pairs of like sex, whereas there was no difference in the rates of spina bifida as between twins from pairs of the same and of differing sex.

In line with previous studies, discordance was found to be the norm, there was

a female preponderance in anencephalus, and females with NTDs were more likely to be born dead than affected males.

As some of the findings in this area of high prevalence have been out of line with previous reports, there is a need to repeat the study. Ideally, this would include information from death certificates and autopsy records. Such a study would clarify the extent to which the findings reflect that the area is of high risk, that there has been a decline in the rate of NTDs since most of the studies were published, or that there have been problems of ascertainment not identified by the approaches employed in the present study.

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