Acta Genet Med Gemellol 40: 337-344 (1991)

Received 6 April 1990
Final 30 July 1991

Birth Defects in Twins: Study in a Spanish Population

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Abstract. The risk for specific defects among twins compared to singletons was studied using data collected by the Spanish Collaborative Study of Congenital Malformations (ECEMC). A total of 136 twins had a major and/or minor congenital defect. The overall rate of congenital defects in twins (2.37%) did not deviate significantly from the rate in singletons (2.21%). Like-sex (LS) and male-male (MM) twin pairs had a slightly higher rate of birth defects than unlike-sex (US) and female-female (FF) pairs, respectively. Defects of the central nervous system, cardiovascular system and genitourinary system were significantly more frequent in LS twins than in singletons, with relative risks of 2.8, 2.5 and 1.6, respectively. No significantly increased risk was found among US twins. Among defects of the central nervous system, the rates of anencephaly, encephalocele and hydrocephaly were significantly higher in total and LS twins; however, no significantly increased risk for spina bifida was observed when compared to singletons. MM twins were also 1.9 times more likely to have hypospadias, but the risk among males of male-female (FM) pairs was decreased.

Key words: Birth defect, Twinning, Neural tube defect, Hypospadias, Epidemiology

INTRODUCTION

Birth defects are a major source of pediatric mortality and morbidity [7]. Despite their clinical and public health importance, much remains to be learned about their etiology. Twin studies have been traditionally considered of great value as a means of elucidating the genetic contribution to the etiology of birth defects. The value of these studies is based on the assumption that twins, whether monozygotic (MZ) or dizygotic (DZ), all have relatively similar intrauterine environment. However, we should take into account that variation in the intrauterine environment (type of chorion, vascular anastomoses, etc) [1,5,10], as well as a possible common etiologic mechanism for twinning and birth defects [23], may be sources of bias in the analysis.

Supported, in part, by a grant from the Servicio Navarro de Salud.

Another limitation lies in the fact that, because both twins and birth defects are rare events, large numbers are needed to provide reliable estimates of the incidence of birth defects. Few studies [9,14,22,23,28] have compared the rate of birth defects in singletons and twins. Some [3,9,11,14,22,23,28,29] have found higher rates for neural tube defects and cardiovascular defects in MZ or like-sex (LS) twins. Furthermore, some authors [29] have reported variation by type of neural tube defect between singletons and twins, suggesting an etiologic mechanism related to twins that is manifested differently for specific birth defects.

The purpose of this study is to provide additional, unbiased data to study the association of twins and birth defects in a Spanish population.

MATERIALS AND METHODS

Data for the study were obtained from the Spanish Collaborative Study of Congenital Malformations (ECEMC), which is a hospital-based study that includes hospitals (45 for this study) from different areas of Spain. Collaborating hospitals were mid-size hospitals with an average of 1,960 births per year (range 600 to 4,000). Since 1976, the ECMEC has collected data on all livebirths with major and/or minor congenital defects detectable during the first three days of life. Data on stillbirths and the total number of twin births started to be collected in 1980. However, further classification of twins in live- and stillborn infants was not recorded. Births monitored yearly by the ECEMC represent approximately 10% of total Spanish births.

A major defect was defined as one having clinical, surgical or cosmetic importance, such as cleft palate. A minor defect was defined as one that does not have clinical, surgical or cosmetic significance, such as small ear tag.

At each hospital, cases were ascertained by a pediatrician with experience in diagnosis of birth defects. The collaborating physician performed a physical exam on each newborn within the first three days of life. Cytogenetic studies were done when a chromosomal anomaly was suspected. Results on other diagnostic procedures (X-rays, autopsy reports, etc) were also available. Mothers of cases and controls underwent a detailed interview which covered pregnancy, family and perinatal data. The study period was January 1980 to March 1985.

Of a total of 337,786 deliveries registered during the study period, 2,874 were reported to be twins. Zygosity was not routinely determined at birth and twins were simply classified as like-sex (LS) or unlike-sex (US).

The rates of congenital defects in twins were compared with the rates in singletons using a chi-square test with 1 degree of freedom. Total malformation rates count each case once, but different specific defect groups may include the same individual more than once if more than one defect was present.

RESULTS

From January 1980 to March 1985, a total of 337,711 livebirths and 2,949 stillbirths were registered. The number of infants with birth defects among twins and signletons in shown in Table 1. During the study period, a total of 7,548 infants were reported to

have a congenital malformation. Among them, 136 were the product of 112 twin pregnancies, 56 being members of MM pairs, 44 of FF pairs, 28 of MF pairs, and 8 of unknown-sex pairs.

The rate of congenital defects in twins (2.37%) did not deviate significantly from that of singletons (2.21%). LS twins had a slightly higher rate (2.34%) than US twins (2.21%); similarly, the rate was higher in MM twins (2.57%) than in FF twins (2.10%), but the difference was not statistically significant.

Table 1 - Total number of twins and singletons included in the sample

	Twins	Singletons	Total
Total no. of births	5,748	334,912	340,660
Infants with birth defects	136	7,412	7,548
Livebirths	126	7,253	7,379
Stillbirths	10	159	169

The prevalence of selected congenital defects in singletons and twins detected during the first three days of life is shown in Table 2. Defects of the central nervous system, cardiovascular system and genitourinary system were significantly more frequent in twins than in singletons, with relative risks of 2.8, 2.5 and 1.6, respectively. No significantly increased risk was found in US twins. Among defects of the central nervous system, the rates of anencephaly, encephalocele and hydrocephaly were significantly higher in total and LS twins; however, the rate of spina bifida in these groups was not significantly higher compared to singletons.

There was an increased rate of esophageal atresia among twins. All four cases were LS twins; other gut atresias were significantly more frequent in US twins. The rate of hypospadias was lower in singletons ($p = 0.01$) than in MM twins, but higher than that observed among males of US pairs ($p > 0.05$).

Cotwins of 23 pairs had at least one congenital defect in common, while in 4 other cases (2 MM and 2 FF pairs) the cotwins had different types of anomalies. The concordance rate was 21% among LS twins (16% among males and 29% among females) and 6% among US pairs. Table 3 shows the numer of concordant and discordant LS and US pairs for some selected birht defects.

DISCUSSION

Differences in the definition and ascertainment of birth defects are responsible, in part, for the variation in the rates of congenital defects observed by different authors. We are aware that, since diagnosis of defects in our study is limited to the first three days of life, the rate of certain defects, such as heart defects, should be underestimated. However, there are two major strenghts in our study: first, good ascertainment of cases,

Table 2 - Prevalence[a] of selected congenital birth defects

Defect category	Twins			Singletons
	LS	US	Total	
Central nervous system	37.4*** (16)	15.8 (2)	33.1*** (19)	13.5 (451)
Spina bifida	9.3 (4)		8.7 (5)	4.5 (152)
Anencephaly	11.7** (5)	7.9 (1)	10.4** (6)	2.8 (94)
Encephalocele	7.0** (3)	7.9 (1)	7.0** (4)	1.2 (41)
Hydrocephaly	16.3*** (7)		12.2*** (7)	3.2 (106)
Cardiovascular system	18.7* (8)		15.7 (9)	7.4 (251)
Skeletal system	81.7* (35)	95.1 (12)	87.0 (50)	102.2 (3482)
Reduction upper limb	7.0 (3)	15.8 (2)	10.4 (6)	4.9 (165)
Reduction lower limb	4.7 (2)	7.9 (1)	7.0 (4)	2.9 (97)
Polydactyly	11.7 (5)	31.7 (4)	15.7 (9)	10.2 (342)
Subluxation heep	16.3** (7)	31.7 (4)	20.9** (12)	48.1 (1623)
Feet abnormalities	25.7 (11)	15.8 (2)	26.1 (15)	24.7 (826)
Digestive system	16.3 (7)	15.8 (2)	17.4 (10)	10.3 (344)
Esophageal atresia	9.3** (4)		7.0** (4)	1.9 (63)
Intestinal stenosis	2.3 (1)	15.8** (2)	7.0** (4)	1.3 (45)
Genitourinary system	56.0** (24)	15.8 (2)	50.5** (29)	30.9 (1035)
Hypospadias[b]	74.7** (16)	15.8 (1)	60.4* (17)	39.0 (643)
Skin	4.7 (2)	39.6 (5)	12.2 (7)	18.2 (609)
Cleft lip +/- palate	7.0 (3)	15.8 (2)	8.7 (5)	5.9 (196)
Cleft palate	7.0 (3)		5.2 (3)	5.2 (173)
Down syndrome	21.0 (9)	7.9 (1)	17.4 (10)	14.6 (490)

[a] Prevalence per 10,000 births.
[b] Prevalence among males.
LS = Like-sex twin pairs; US = Unlike-sex twin pairs.
* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

https://doi.org/10.1017/S0001566000003524 Published online by Cambridge University Press

Table 3 - Number of concordant and discordant twin pairs for selected birth defects

Defect category		Concordant pairs	Discordant pairs
Spina bifida	LS	0	4
	US	0	0
Anencephaly	LS	0	5
	US	0	1
Encephalocele	LS	1	1
	US	0	1
Hypospadias	LS	3	10
	US	0	1
Cleft lip +/- palate	LS	1	1
	US	0	2
Polydactyly	LS	1	3
	US	0	4
Down syndrome	LS	4	1
	US	0	1

LS = Like-sex twin pairs; US = Unlike-sex twin pairs.

as infants were all carefully examined at birth by a pediatrician with experience in diagnosis of birth defects; and second, the large sample size of the study, which provides data on specific defects with relatively low prevalence in the population.

In general, there is consistent evidence that birth defects are more common among twins than singletons [3,9,11,14,16,22,23,29]. Some studies [12,27,28], including ours, could not demonstrate a significantly higher rate of malformations among twins vs singletons. However, our data on specific categories of defects support the idea that the increased risk that twins may have for congenital defects is limited to LS or MZ twins. Moreover, such risk seems to be limited to certain defect categories involving the central nervous system, cardiovascular system and genitourinary system.

As shown in Table 1, we observed that the proportion of infants with congenital anomalies born dead was higher in twins (7.4%) than in singletons (2.1%). Similar observations were reported by Myrianthopoulos in 1975 [22]; the frequencies, however, were lower (3.2.% among twins and 1.0% among singletons) than in this study. Several explanations can be put forward:

a) Stillborn twins might be more likely to undergo examination than stillborn singletons, or examination of twins might be more extensive than that of singletons. The lack of differences in rates of congenital anomalies between twins and singletons, however, suggests that ascertainment bias is not a severe problem in this study.

b) Twin individuals with congenital malformations might be more likely to die in utero than singletons with congenital anomalies. Twin development, in general, is influenced by different environmental factors (restricted uterine-placental blood flow,

placental vascular anastomosis, higher frequency of preeclampsia, and umbilical cord anomalies, etc) [2,26] which may partially explain the general growth retardation [24] and the higher rate of stillbirths [1] and abortions [20] in twins. On the other hand, the twinning process, as well as some of these environmental factors, have been held to cause certain malformations in MZ twins (fetus papyraceous, fetus amorphus, anencephaly, etc), and usually consequent intrauterine death [25]. In fact, in our small sample of twin babies born dead with congenital malformations, two were fetus amorphus and two had anencephaly. Finally, we think it is likely that a twin with a congenital defect, in addition to the general tendency to be growth-retarded, may be more vulnerable to environmental factors and, therefore, more likely to die in utero than a singleton with the same anomaly.

Most studies [8,9,11,14,22,23] have reported an increased rate of neural tube defects (NTD) in twins vs singletons. However, such association between NTD and twinning has not been consistently found in high-prevalence NTD areas [4]. By type of NTD, anencephaly and encephalocele appear to be most frequently associated with twinning, while spina bifida does not [14,29]. Windham an Bjerkadal [29] suggested that if MZ twins are more susceptible to environmental agents, then lower exposures might be sufficient to interfere with NTD in twins but not in singletons. Therefore, an excess of twin cases might be expected in low-NTD prevalence areas, while in areas of high prevalence more singletons would be affected and obscure the association with twinning. Our study shows that in our population, which is a low-NTD prevalence area, there is an increased rate of anencephaly and encephalocele in twins, but not of spina bifida. These findings support the idea [29] of a different etiological mechanisms of anencephaly and spina bifida, perhaps related to twinning, as also suggested by their different epidemiology [15].

An excess of hydrocephalus in twins has been shown in different studies [9,12,28], including ours. The high rate of this congenital defect, and perhaps those affecting the genitourinary and cardiovascular systems, might partly reflect the higher rate of prematurity and low birthweight in twins. In our sample, hydrocephalus was 2.6 times more frequent among twins under 2,500 g than in singletons of the same weight. However, the difference was not statistically significant. For defects of the genitourinary system, the risk among twins of low birthweight was nine times higher ($p < 0.001$) than in singletons of the same weight. Preterm twin infants (< 40 weeks of pregnancy) had not a significantly higher risk for such defects compared to singletons of the same gestational age.

Despite differences in ascertainment, the finding of an excess rate of cardiovascular defects among twins, which seems to be confined to LS twins, is consistent with other reports [9,14,18,19]. The relatively small number of cardiovascular defects detectable during the first three days of life, and the lack of specific diagnosis in some instances (three cases in this study), make it more difficult to compare our results to previous studies. Five infants had a structural cardiac defect (2 had a common atrioventricular canal, 1 a ventricular septal defect, 1 atresia of a cardiac valve, 1 transposition of the great vessels) and 1 had dextrocardia. No cases with patent ductus arteriosus were reported.

The association between twinning and hypospadias is also controversial. While some authors [6,17,19,21] have described an increased risk among twins vs singletons, some large studies have failed to show that association [11,22]. Furthermore, a decreased risk

in male twins of US pairs has been observed in some European and South European populations [13]. Our data confirm that MM pairs have a higher risk for hypospadias than singletons, while the risk for males of LS pairs seems to be lower. Unfortunately, we cannot provide data on the risk for MZ vs DZ-MM pairs. Therefore, the question as to whether the increased risk for hypospadias among twins is associated with monozygozity or MM pairs still remains unclear.

In contrast with the findings reported by other authors [14,19,28], we observed a slightly higher rate of Down syndrome in twins than in singletons. This finding is likely to be attributable to maternal age effect as 5 of our 6 pairs with Down syndrome were born to a mother above 35 years of age. In fact, in our population (data not shown), the proportion of mothers above 35 years of age is higher in twins than in singletons (27% vs 11%).

Concordance rate for any birth defect was higher, but not statistically significant, among LS pairs (21%) than US pairs (6%). Three of the 13 twin pairs (23%) with hypospadias were concordant for that malformation. On the contrary, all cases of spina bifida and anencephaly were discordant. Nevertheless, numbers are too small to draw firm conclusions regarding concordance rates for specific birth defects, and further studies are needed to provide reliable estimates.

CONCLUSION

Our study shows a similar overall rate of birth defects in twins and singletons. On the other hand, data on specific defects suggest that twins are more susceptible to birth defects of the central nervous system (anencephaly, encephalocele and hydrocepahly, but not spina bifida), cardiovascular system and genitourinary system.

It appears that the risk for hypospadias is higher in MM pairs and lower in MF pairs. Additional studies should be carried our in an attempt to understand the possible etiological mechanism of hypospadias and other specific birth defects related to twinning.

Acknowledgements: The author wishes to thank the pediatricians at the collaborating hospitals for their participation in the study.

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