

ORIGINAL ARTICLE

Fetal or infant death in twin pregnancy: neurodevelopmental consequence for the survivor

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Aim: To determine the neurodevelopmental morbidity in the surviving twin after fetal or infant death of the co-twin.

Methods: Twin pregnancies with an antepartum or infant death delivered between 1981 and 1992 were identified from the Northern Perinatal Mortality Survey. Information on the neurodevelopmental morbidity of infant survivors of a deceased co-twin was obtained by a questionnaire sent to the community paediatrician or general practitioner.

Results: A total of 111 children who survived infancy after the fetal death of the co-twin (group 1) and 142 from liveborn twin pairs in which one twin died in infancy (group 2) were traced. Responses were received from 97 (87%) and 130 (92%) respectively. In group 1, the cerebral palsy prevalence was 93 (95% confidence interval (CI) 43 to 169) per 1000 infant survivors; it was more common in like-sex pairs (8/70) with a prevalence of 114 (95% CI 51 to 213) compared with 45 (95% CI 1 to 228) per 1000 infant survivors in unlike-sex pairs (1/22). The overall prevalence of neurodevelopmental morbidity (including developmental delay) was 175 (95% CI 106 to 266) per 1000. In group 2, the cerebral palsy prevalence was 154 (95% CI 84 to 223) per 1000 infant survivors in like-sex (16/104) and 77 (95% CI 9 to 251) in unlike-sex (2/26) survivors; the overall prevalence of neurodevelopmental morbidity was 246 (95% CI 172 to 320) per 1000.

Conclusions: The risk of cerebral palsy is increased in the surviving twin after a fetal or infant co-twin death compared with the general twin population. Like-sex twins are at greater risk than unlike-sex. The probable cause, in addition to the consequences of prematurity, is twin-twin transfusion problems associated with monochorionicity.

Twins are at a higher risk than singletons, not only for fetal and infant mortality, but also neurological morbidity. The prevalence of cerebral palsy ranges from 7–12 per 1000 infant survivors in twins compared with 1–2 in singletons.^{1–5} The higher relative risk of cerebral palsy for twins is not entirely attributable to the overrepresentation of low birth-weight and preterm infants, as the risk is also higher for normal birthweight twins than for comparable singletons.^{2 5 6}

Case reports and hospital based case series have found that the antenatal death of a twin is associated with severe morbidity in the co-twin.^{7–14} Over the last decade, population based studies have also shown that, among twin pregnancies with an antenatal loss of one twin, the surviving twin has an increased rate of cerebral palsy compared with twin pregnancies in which both twins survived.^{1 2 6 15 16} In the case reports it has been found that monochorionic twins are at particularly high risk.^{12 17–26} However, there is a lack of population based follow up studies of the surviving twin whose co-twin died in utero that include data on placentation and gestational age.

The aim of this population based follow up study was to determine the neurodevelopmental morbidity for the surviving twin of a co-twin fetal or infant death.

METHODS

Study sample

All twin pregnancies delivering between 1981 and 1992 with an antepartum or infant death were identified from the population based Northern Perinatal Mortality Survey (PMS). Since its inception in 1981, the PMS has collected data on all late fetal losses, stillbirths, and infant deaths occurring to mothers resident in the former Northern Region of England.^{27 28} Notifications of death are made by multiple

sources. The years 1981–1992 were selected to complement a national study of the consequences of intrauterine death in twin pregnancies for the survivor, which covered the years 1993–1995.¹⁶

Infant survivors (children who survived beyond the first year of life) from twin pairs in which there has been a fetal death (group 1), and infant survivors from liveborn twin pairs in which one infant died in infancy (group 2), comprised two study groups.

Definitions

Fetal death was defined as a spontaneous (identifiable) intrauterine death which was delivered after 28 completed weeks gestation (the legal limit of fetal viability in the United Kingdom during the study period). Infant death was defined as a live birth that died within the first 365 days of life. The definition of cerebral palsy was that proposed by the members of the Little Club²⁹ and updated by Bax.³⁰ Postneonatally acquired cases were excluded. "Other cerebral impairment" is used for children with evidence of cerebral impairment other than cerebral palsy—for example, learning disability, epilepsy, sensory neural hearing loss, general developmental delay.

Ethical approval

Ethical approval was obtained from the multicentre research ethics committee and from all the local research ethics committees within the Northern Region.

Abbreviations: PMS, Northern Perinatal Mortality Survey; CI, confidence interval.

Table 1 Causes of death among live births whose co-twin was a fetal or infant death

Gestational age (weeks)	BW of fetal death* (g)	Registered cause of fetal death*	BW of live birth (g)	Cause of death in liveborn twin	Age at death	Sex of the pair/chorionicity
Causes of death in the liveborn twin of a co-twin fetal death						
28	595	TTT syndrome	1235	TTT syndrome; pulmonary immaturity; IVH	7 days	MM/MC
29	1600	TTT syndrome	1140	TTT syndrome	18 days	MM/MC
29	Unknown	Fetus papyraceous	1500, male	Renal agenesis	1 hour	unknown
30	990	TTT syndrome	1179	TTT syndrome; extensive white matter infarction	32 days	FF/MC
31	2795	Acardia; anencephaly; multiple anomalies	1470	TRAP sequence	1 day	MM/MC
32	1475	TTT syndrome	1635	TTT syndrome	14 days	MM/MC
34	2620	TTT syndrome	1670	TTT syndrome	14 hours	FF/MC
36	477	Acardia; anencephaly	2000	Congenital cardiac anomaly	40 days	FF/MC
38	Unknown	Fetus papyraceous	2190	TTT syndrome; microcephaly; cerebral palsy	102 days	FF/MC
39	1280	IUGR, macerated fetus	1180	Respiratory obstruction; epileptic fit; cerebral palsy	11 years	FF/unknown
40	2780	Antepartum anoxia	4000	Intrapartum anoxia	7 days	MM/MC
40	2360	Antepartum anoxia	3360	Intrapartum anoxia	5 minutes	ULS/DC
Causes of death in childhood in infant survivors whose co-twin was an infant death						
26	790	HMD, IVH	690	Cardiac arrest; bronchopneumonia; bronchopulmonary dysplasia	13 months	FF/unknown
38	2090	Coarctation of aorta	2295	Respiratory arrest; sleep apnoea; cerebral palsy	7 years	MM/unknown
36	2010	Miscellaneous (inborn error)	2110	Niemann-Pick disease	13 years	MM/unknown

*Refers to infant death in infant death plus infant survivor group.

BW, Birth weight; TTT, twin-twin transfusion; TRAP, twin reversed arterial perfusion; MM, male-male; FF, female-female; ULS, unlike sex; MC, monochorionic; DC, dichorionic; HMD, hyaline membrane disease; IVH, intraventricular haemorrhage; IUGR, intrauterine growth retardation.

Follow up

Infant survivors from both study groups were cross checked with a register of cerebral palsy, comprising children born in three health districts of the Northern Region (Newcastle, Northumberland, and North Tyneside) before 1991.³¹ For children born in 1991–1992, infant survivors were cross validated against the North of England Collaborative Cerebral Palsy Survey, which covers all births in the Northern Region from 1991. Using death notifications, deaths up to age 16 years were identified.

A questionnaire on the long term (minimum 7 years of age) disability was sent to the community paediatricians except for those children who were known to have cerebral palsy from the regional register or who had died in childhood. The community paediatricians identified children with moderate and severe disability using the local register of children with disability or the special needs register. For those districts where there was no special needs register or no clear information on the health status of the children during their first seven years of life, the same questionnaire was sent to the child's general practitioner. If the current registration with a general practitioner was unavailable from the local health authority because the family had moved, or the name of the child had been changed, the contact details of the general practitioner were obtained from the Office for National Statistics.

Questionnaire

The questionnaire comprised five questions: is the child known to have any disability—for example, hearing, vision, physical? Is the child known to have cerebral palsy—for example, diplegia, hemiplegia, quadriplegia, dyskinetic, mixed? Is the child known to have congenital abnormality—for example, neural tube defect, cleft palate, chromosomal abnormality? Is the child known to have developmental delay? Are there any other relevant observations? If the answer was positive to any of the questions, the general practitioner was asked to specify further details.

Chorionicity

Unlike-sex twins were assumed to be dizygotic and therefore dichorionic. Like-sex twins may be dizygotic (always dichorionic) or monozygotic (monochorionic or dichorionic). Data on chorionicity for like-sex twin pregnancies, based on clinical or

pathological examination of placenta or evidence of twin-twin transfusion syndrome (polyhydramnios/oligohydramnios, birthweight discordancy, intertwin haemoglobin discrepancy, or anaemic/plethoric co-twins), were obtained from the PMS or hospital records.

Statistical analysis

Descriptive analysis was carried out using the Statistical Package for the Social Sciences (SPSS for Windows).³² Cerebral palsy prevalence among twin survivors was calculated per 1000 infant survivors. Cerebral palsy prevalence among singletons in North East England in 1985–1989 was calculated per 1000 neonatal survivors (P Drummond, personal communication). Confidence intervals were calculated using the Confidence Interval Analysis package.³³ χ^2 tests were used to test differences in proportions. Statistical significance was accepted at the $p < 0.05$ level.

RESULTS

Mortality in the liveborn co-twin of a fetal or infant death

In 1981–1992, there were approximately 9520 twin births (4760 pregnancies) (Office for National Statistics data. As the number of twin births for 1981 was unavailable, the number has been estimated assuming the same number of twin births in 1981 as in 1982.). In 34 pregnancies, both twins died in utero; in 130, one twin was a fetal death and the co-twin a live birth, and 11 of these live births died in infancy. Table 1 shows the certified causes of death of both the fetus and the liveborn infant in these 11 twin pairs. The majority (9/11) had monochorionic placentation (six had clinical evidence of twin-twin-transfusion syndrome, in two the fetal death was an acardiac twin, and in one there was histological evidence of monochorionicity).

There were 119 co-twins of a fetal death who survived infancy; these comprised group 1. One of these live births who survived infancy in whom the cause of death was certified as cerebral palsy, died aged 11 years (table 1).

In 92 pregnancies both twins died in infancy. In 150 pregnancies, one twin died in infancy and the co-twin survived. These comprised group 2; of the 150 infant survivors, three died in childhood, one of whom had cerebral

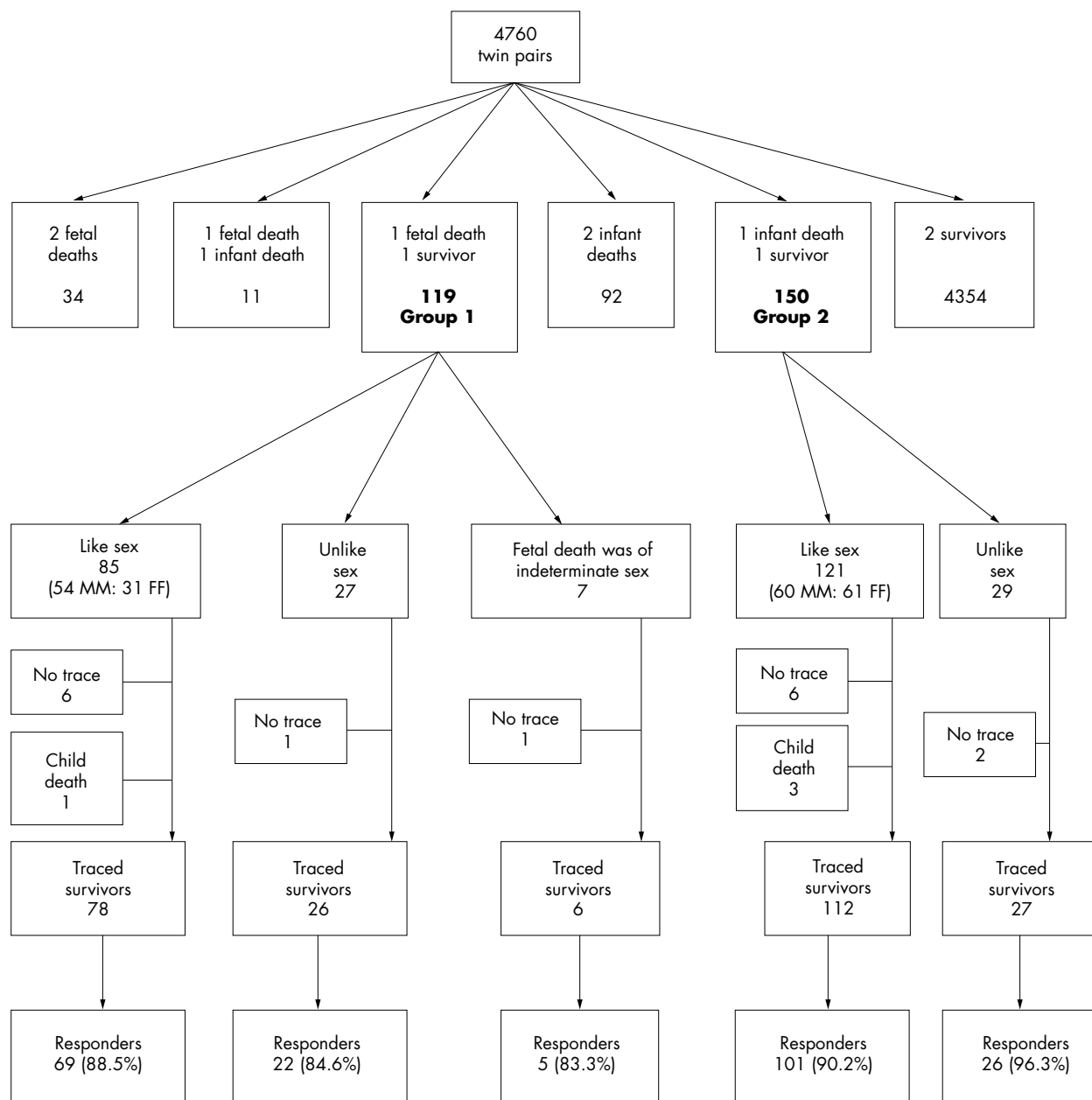


Figure 1 Number of twin pairs with different outcome born in 1981–1992, infant survivors of a co-twin fetal death (group 1) and a co-twin infant death (group 2), and the response rate for the survivors beyond 7 years of age.

palsy as the certified cause of death (table 1). Figure 1 shows the derivation of the study sample.

The following analysis considers group 1 and group 2 infant survivors only.

Response rates

Figure 1 shows the response rates for the surviving co-twins of like-sex and unlike-sex pairs in groups 1 and 2. In seven cases, the sex of the fetal death was indeterminate, and there were eight children in each of groups 1 and 2 who could not be followed up because they were adopted, had migrated, or were not registered with a general practitioner. Non-response arose from the refusal of general practitioners to seek parental permission or the parents refusing consent to release information on the health status of their child.

Group 1: infant survivors of a co-twin fetal death

There were nine cerebral palsy cases out of the 97 (96 responders and one child death) infant survivors, a cerebral

palsy prevalence of 93 (95% confidence (CI) 43 to 169) per 1000 infant survivors. Eight of the children with cerebral palsy were from 70 like-sex pairs, a prevalence of 114 (95% CI 51 to 213) per 1000 infant survivors. There was one case of cerebral palsy among 22 unlike-sex pairs, a cerebral palsy prevalence of 45 (95% CI 1 to 228) per 1000 infant survivors. Table 2 shows pregnancy and birth details for like-sex and unlike-sex fetal deaths and the surviving co-twins with cerebral palsy. It is worth noting that in the single case of cerebral palsy among unlike-sex twins, the twin who died in utero weighed only 500 g, and the death certificate specified that the fetus was severely macerated. In such circumstances, it is possible that the sex of the fetus was incorrectly assigned. In like-sex twins, placentation was predominantly monochorionic (at least five of the eight cases).

In addition to those children with cerebral palsy, eight of the 97 survivors had evidence of other cerebral impairment (table 3). Six were from like-sex pairs, a prevalence of 86 (95% CI 32 to 177) per 1000 infant survivors, and two from

Table 2 Cerebral palsy in the surviving twin of like-sex and unlike-sex fetal death co-twin (group 1)

Gestational age (weeks)	BW of fetal death (g)	Registered cause of fetal death	Sex of live birth	BW of live birth (g)	Cerebral palsy type	Type of placentation
Survivors from like-sex twin pairs						
30	920	TTT syndrome	M	1440	Diplegia	MC
33	90	APA, severe maceration	M	1786	Quadriplegia	MC
33	910	IUGR, APA	F	1635	Quadriplegia	MC
36	280	Missed abortion	F	2380	Quadriplegia	Placenta not examined
36	2070	APA, severe maceration	M	2200	Hemiplegia	MC
37	480	TTT syndrome	M	3320	Quadriplegia	MC
38	1860	APA, gross maceration	F	2560	Hemiplegia	DC
39	1280	IUGR, macerated fetus	F	1180	Athetoid	Placenta not examined
Survivors from unlike-sex twin pairs						
30	500	APA, advanced maceration	M	1300	Diplegia	Placenta not examined

BW, Birth weight; IUGR, intrauterine growth retardation; APA, antepartum anoxia; MC, monochorionic; DC, dichorionic; TTT, twin-twin transfusion.

Table 3 Other cerebral impairment in the surviving twin of like-sex and unlike-sex fetal death co-twin (group 1)

Gestational age (weeks)	BW of fetal death (g)	Registered cause of fetal death	Sex of live birth	BW of live birth (g)	Type of placentation	General practitioner comments on the surviving twin
Survivors from like-sex twin pairs						
29	875	APA	M	1230	MC	Severe difficulties in both receptive and expressive language abilities
30	1900	TTT syndrome	F	1100	MC	Sensory neural hearing loss, epilepsy
31	380	APA	M	1600	Placenta not examined	Developmental delay
32	1120	APA	M	1970	DC	Difficulty with coordination and fine manipulation skills
33	1305	APA	F	1380	Placenta not examined	Sensory neural hearing loss
35	1080	Congenital anomaly (miscellan. syndrome)	M	2060	DC	Delay in language development
Survivors from unlike-sex twin pairs						
32	310	APA	M	1910	DC	Learning difficulties
33	250	APA	M	1320	Placenta not examined	Hearing loss, dyspraxia

BW, Birth weight; IUGR, intrauterine growth retardation; APA, antepartum anoxia; MC, monochorionic; DC, dichorionic; TTT, twin-twin transfusion.

unlike-sex pairs, a prevalence of 91 (95% CI 11 to 292) per 1000 survivors.

Combining the data in tables 2 and 3, the total cerebral impairment prevalence is 175 (95% CI 106 to 266) per 1000 infant survivors: 200 (95% CI 114 to 313) for like-sex and 136 (95% CI 29 to 349) for unlike-sex survivors.

Group 2: infant survivors of a co-twin infant death

There were 18 cerebral palsy cases among the 130 (127 responders and three child deaths) group 2 infant survivors, a cerebral palsy prevalence of 138 (95% CI 79 to 198) per 1000 infant survivors: 154 (95% CI 84 to 223) in like-sex (16/104) and 77 (95% CI 9 to 251) in unlike-sex (2/26) infant survivors (table 4).

In addition to those with cerebral palsy, there were 14 children with evidence of other cerebral impairment; 13 were from like-sex pairs, a prevalence of 125 (95% CI 61 to 189) per 1000 infant survivors, and one from unlike-sex pairs, a prevalence of 38 (95% CI 1 to 196) (table 5).

Combining the data in tables 4 and 5, the total cerebral impairment prevalence is 246 (95% CI 172 to 320) per 1000 infant survivors: 279 (95% CI 193 to 365) for like-sex and 115 (95% CI 24 to 302) for unlike-sex survivors.

Gestational age specific cerebral palsy rates

Table 6 shows the gestational age specific cerebral palsy rates for like-sex and unlike-sex survivors. Group 2 survivors, compared with group 1, were more likely to be born very preterm (41% v 12% before 32 weeks of gestation). In both groups, gestational age specific cerebral palsy rates in the survivors

were considerably higher than those in singletons. Differences in gestational age specific cerebral palsy rates between group 1 and group 2 survivors in corresponding gestational age groups were not statistically significant, partly because of the small numbers.

DISCUSSION

This population based regional study, following up twins born during 1981–1992, complements a national study of the consequences for the surviving twin of fetal or infant death of the co-twin born between 1993 and 1995.^{16–34} Although smaller than the national study, it has a number of advantages. Firstly, recording the sex of a fetal death is likely to be more accurate because it is based on the information derived from the hospital notes and reports of the postmortem examination. In the national birth registration system, there are problems in coding of the sex of a fetal death, especially if it was a fetus papyraceus.³⁵ If the sex of a fetus papyraceus was indeterminate, it was always coded as male in the national statistics; furthermore, the parents may be allowed to decide which sex is recorded on the death certificate. Secondly, information on chorionicity was available in this study for most like-sex fetal death/survivor pairs (group 1) with cerebral palsy. Thirdly, there was a better response rate and a longer period of follow up. The longer follow up increased the likelihood of learning disability in the absence of motor disability being recognised.

The response rate was high, 87% for group 1 and 92% for group 2; nevertheless, non-response bias should be considered. Assuming that none of the untraced children and

Table 4 Cerebral palsy in the surviving twin of like-sex and unlike-sex co-twin who died in infancy (group 2)

Gestational age (weeks)	BW of infant death (g)	Registered cause of infant death	Sex of survivor	BW of survivor (g)	Cerebral palsy type
Survivors from like-sex twin pairs					
24	500	Pulmonary immaturity	M	580	Diplegia
25	760	HMD	M	620	Diplegia
25	545	HMD, TTTS	M	750	Diplegia
25	630	HMD	F	760	Right hemiplegia
26	950	HMD	M	975	Quadriplegia
27	660	IVH, leucomalacia, TTTS	F	865	Diplegia
28	1340	HMD with IVH	M	1300	Diplegia
28	1020	HMD with IVH	F	960	Diplegia
28	980	HMD with IVH	M	1155	Left hemiplegia
29	1235	HMD with infection	M	1080	Diplegia
30	630	Neonatal infection	F	1555	Diplegia
31	1420	HMD	F	1420	Diplegia
31	1420	Trisomy 13, encephalocele	F	1110	Asymmetric quadriplegia
32	1605	HMD, necrotising enterocolitis	M	1550	Asymmetric diplegia
34	1450	HMD with IVH	M	1590	Quadriplegia
38	2090	Coarctation of aorta	M	2295	Quadriplegia
Survivors from unlike-sex twin pairs					
28	985	HMD with IVH	M	1050	Diplegia
31	1610	HMD with infection	F	1275	Quadriplegia

Type of chorionicity was available only for a few cases, therefore not presented in the table.

BW, Birth weight; HMD, hyaline membrane disease; IVH, intraventricular haemorrhage; TTTS, twin-twin transfusion syndrome.

Table 5 Other cerebral impairment in the surviving twin of like-sex and unlike-sex co-twin who died in infancy (group 2)

Gestational age (weeks)	BW of infant death (g)	Registered cause of infant death	Sex of survivor	BW of survivor (g)	General practitioner comments on the surviving twin
Survivors from like-sex twin pairs					
24	927	HMD	M	795	Reduced intellectual development
26	720	Intrapartum asphyxia	F	760	Motor impairment, learning difficulties
28	1180	HMD with IVH	F	1100	Mild learning disability, severe psychological problems
29	620	TTTS, HMD	M	1215	Mild learning difficulties, scaphocephaly
29	1300	Neonatal infection	M	1308	Delay in receptive and expressive language, learning difficulties
29	1140	HMD with IVH	M	950	Mild problems with coordination affecting left side, special needs in teacher for reading
31	1620	Viral meningitis	F	1755	Learning difficulties
31	1560	Birth trauma	M	1180	Severe learning difficulties
32	1490	Neonatal infection	F	1515	Low intellectual development
33	2030	SIDS	F	2070	Mild learning disability
33	1400	Intrapartum asphyxia	M	1440	Learning disability
34	1800	Spina bifida, hydrocephalus	M	2100	Learning disability
38	3055	Birth trauma	M	3205	Speech delay
Survivors from unlike-sex twin pairs					
28	1350	HMD with IVH	F	1135	Epilepsy, behaviour problems, retinopathy of prematurity

Type of chorionicity was available only for a few cases, therefore not presented in the table.

BW, Birth weight; HMD, hyaline membrane disease; IVH, intraventricular haemorrhage; TTTS, twin-twin transfusion syndrome; SIDS, sudden infant death syndrome.

non-responders had cerebral palsy or other cerebral impairment, the disability rate would have been marginally lower at 143 per 1000 for group 1 and 213 per 1000 for group 2. These prevalences remain extremely high when compared with the generality of cerebral palsy prevalence in twins.³

We were unable to collect complete information on chorionicity, as there was no record of pathological examination of the placenta in many cases of like-sex twins in group 2.

Ideally, the prevalence of serious neurological morbidity among infant survivors of a fetal death should be compared with morbidity prevalence in liveborn twin pairs when both twins survived infancy. This was impractical as it would have entailed following up over 9000 twins born in 1981–1992.

The surviving twin of a co-twin fetal death (group 1) was found to be at high risk of either dying in infancy or having

serious neurodevelopmental morbidity. The overall prevalence of serious neurodevelopmental morbidity was 175 per 1000 infant survivors. The cerebral palsy prevalence in like-sex twins was over twice that in unlike-sex twins, although this difference was not statistically significant. In the light of other reports, this is probably a consequence of vascular anastomoses that occur with monochorionic placentation.^{8 19 21 24–26} Twin-twin transfusion syndrome is limited to monochorionic twins, and the cerebral impairment probably has a haemodynamic cause. Indeed, the placentation was predominantly monochorionic in the like-sex group of cerebral palsy cases, providing further evidence that twin-twin transfusion problems are the underlying cause of the cerebral damage in this group.

The cerebral palsy rate in survivors of a co-twin fetal death in this study is in accordance with the findings of previously

Table 6 Gestational age specific cerebral palsy (CP) prevalence rates in surviving co-twin of a fetal (group 1) or infant (group 2) death per 1000 infant survivors

Gestational age (weeks)	Survivor of a fetal death co-twin (group 1)				Survivor of a co-twin who died in infancy (group 2)			
	No with CP	No of responders	CP rate (per 1000 survivors)	95% CI	No with CP	No of responders	CP rate (per 1000 survivors)	95% CI
Like-sex twins								
<32	1	9	111.1	3 to 482	13	43	302.3	172 to 461
≥32	7	61	114.8	47 to 222	3	61	49.2	10 to 137
Total	8	70	114.3	51 to 213	16	104	153.8	84 to 223
Unlike-sex twins								
<32	1	2	500.0	13 to 987	2	11	181.8	23 to 519
≥32	0	20	–	NA	0	15	–	NA
Total	1	22	45.4	1 to 228	2	26	76.9	9 to 251

Note: Gestational age specific cerebral palsy prevalence in singletons in the NE England Register (1985–1989) were: <32 weeks 62.1 (95% CI 39 to 93); ≥32 weeks 1.7 (95% CI 1.3 to 2.0) per 1000 neonatal survivors (P Drummond, personal communication). NA, Not applicable.

published population based studies,^{1–3 6 16} except one Swedish follow up study of a similar cohort of twin survivors after a fetal death of a co-twin.¹⁵ In that study (50% were lost to follow up), the disability rate at the age of 8 years was 46 per 1000 (3 of 65). This rate was about half of that found in this and other referred studies. The disparity in the disability rates may be due to differences in methodology (definitions, exclusions, denominators, etc).

In group 2 survivors, the proportion of infants born before 32 weeks gestation was disproportionately high. Three possible pathways leading to cerebral impairment in very preterm infants have been proposed.³⁶ Prematurity per se may predispose to hypoxic-ischaemic and haemorrhagic cerebral damage; an antenatal factor may cause both the cerebral impairment and lead to preterm delivery; an antenatal factor may cause the cerebral impairment that predisposes to preterm delivery. When both twins are live births and one dies in infancy (group 2), the cause of death is prematurity in the vast majority. The surviving co-twin in each case therefore is liable to the complications of prematurity. Very preterm birth—that is, birth before 32 completed weeks of gestation, as defined by the WHO³⁷—is considered the strongest predictor of later cerebral palsy, with a higher risk associated with a lower gestational age at delivery.³⁶ A prospective population based study of extremely preterm infants (22–25 completed weeks of gestation) in the United Kingdom and Ireland showed that 49% of the survivors had disability at 30 months of corrected age, with nearly half of them being severely disabled.³⁸ Our study found a high cerebral palsy prevalence in group 2 infant survivors. Among disabled survivors in this group, the proportion of those born before 32 weeks gestation was 83% (15/18). In this group, prematurity is likely to be the leading factor in the development of cerebral palsy. The cerebral palsy and other cerebral impairment attributable to the prematurity per se, the first pathway, will account for some of the neurological morbidity in both like-sex and unlike-sex twins. However, in addition to the consequences of prematurity, there is an excess morbidity in like-sex twins. In such cases, the two other pathways mentioned above, with twin-twin transfusion as an antenatal factor, may contribute to both the cerebral impairment and the preterm delivery.

Given the importance of chorionicity, both for the management of twin pregnancies and research into the causes of cerebral palsy, it needs to be emphasised again that the accurate antenatal determination of chorionicity with postnatal confirmation is crucial.

Only about 10% of cases of cerebral palsy are of intrapartum origin,³⁹ and research into the causes of cerebral palsy needs to focus on antepartum events.⁴⁰ In multiple pregnancies, the effect of the timing of an intrauterine death on the outcome and prognosis for the surviving co-twin is still controversial.

The current study did not address the effects of fetal loss in the first trimester of pregnancy (the vanishing twin), which would in theory have an adverse consequence for the survivor. Studies addressing this have so far produced conflicting evidence,^{13 18 41 42} and a prospective study of survivors from twin pregnancies with a confirmed co-twin loss in the first trimester of pregnancy should determine the significance of this event for the surviving co-twin.

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REFERENCES

- 1 Pharoah POD, Cooke T. Cerebral palsy and multiple births. *Arch Dis Child Fetal Neonatal Ed* 1996;**75**:F174–7.
- 2 Petterson B, Nelson KB, Watson L, et al. Twins, triplets, and cerebral palsy in births in Western Australia in the 1980s. *BMJ* 1993;**307**:1239–43.
- 3 Williams K, Hennessy E, Alberman E. Cerebral palsy: effects of twinning, birth weight, and gestational age. *Arch Dis Child Fetal Neonatal Ed* 1996;**75**:F178–82.
- 4 Yokoyama Y, Shimizu T, Hayakawa K. Prevalence of cerebral palsy in twins, triplets and quadruplets. *Int J Epidemiol* 1995;**24**:943–8.
- 5 Touyama M, Ochiai Y, Touyama J. Cerebral palsy in twins in Okinawa. *No To Hattatsu* 2000;**32**:35–8.
- 6 Grether JK, Nelson KB, Cummins SK. Twinning and cerebral palsy: experience in four northern California counties, births 1983 through 1985. *Pediatrics* 1993;**92**:854–8.
- 7 Axt R, Mink D, Hendrik J, et al. Maternal and neonatal outcome of twin pregnancies complicated by single fetal death. *J Perinat Med* 1999;**27**:221–7.
- 8 Burke MS. Single fetal demise in twin gestation. *Clin Obstet Gynecol* 1990;**33**:69–78.
- 9 Chen FJ, Villarreal Peral C, Juarez Azpilcueta A. Twin pregnancy complicated by one intrauterine fetal death. Report of a case and review of the literature. *Ginecol Obstet Mex* 1995;**63**:352–5.
- 10 Carlson NJ, Towers CV. Multiple gestation complicated by the death of one fetus. *Obstet Gynecol* 1989;**73**:685–9.
- 11 Enbom JA. Twin pregnancy with intrauterine death of one twin. *Am J Obstet Gynecol* 1985;**152**:424–9.

- 12 **Weig SG**, Marshall PC, Abrams IF, *et al.* Patterns of cerebral injury and clinical presentation in the vascular disruptive syndrome of monozygotic twins. *Pediatr Neurol* 1995;**13**:279–85.
- 13 **Prompeler HJ**, Madjar H, Klosa W, *et al.* Twin pregnancies with single fetal death. *Acta Obstet Gynecol Scand* 1994;**73**:205–8.
- 14 **Liu S**, Benirschke K, Scioscia AL, *et al.* Intrauterine death in multiple gestation. *Acta Genet Med Gemellol (Roma)* 1992;**41**:5–26.
- 15 **Rydhstrom H**, Ingemarsson I. Prognosis and long-term follow-up of a twin after antenatal death of the co-twin. *J Reprod Med* 1993;**38**:142–6.
- 16 **Pharoah POD**, Adi Y. Consequences of in-utero death in a twin pregnancy. *Lancet* 2000;**355**:1597–602.
- 17 **Melnick M**. Brain damage in survivor after in-utero death of monozygous co-twin. *Lancet* 1977;**2**:1287.
- 18 **Anderson RL**, Golbus MS, Curry CJ, *et al.* Central nervous system damage and other anomalies in surviving fetus following second trimester antenatal death of co-twin. Report of four cases and literature review. *Prenat Diagn* 1990;**10**:513–18.
- 19 **Fusi L**, Gordon H. Twin pregnancy complicated by single intrauterine death. Problems and outcome with conservative management. *Br J Obstet Gynaecol* 1990;**97**:511–16.
- 20 **Bejar R**, Vigliocco G, Gramajo H, *et al.* Antenatal origin of neurologic damage in newborn infants. II. Multiple gestations. *Am J Obstet Gynecol* 1990;**162**:1230–6.
- 21 **Bajoria R**, Wee LY, Anwar S, *et al.* Outcome of twin pregnancies complicated by single intrauterine death in relation to vascular anatomy of the monochorionic placenta. *Hum Reprod* 1999;**14**:2124–30.
- 22 **Benirschke K**. Intrauterine death of a twin: mechanisms, implications for surviving twin, and placental pathology. *Semin Diagn Pathol* 1993;**10**:222–31.
- 23 **Gaucherand P**, Rudigoz RC, Piacenza JM. Monofetal death in multiple pregnancies: risks for the co-twin, risk factors and obstetrical management. *Eur J Obstet Gynecol Reprod Biol* 1994;**55**:111–15.
- 24 **Yoshida K**, Matayoshi K. A study on prognosis of surviving cotwin. *Acta Genet Med Gemellol (Roma)* 1990;**39**:383–8.
- 25 **Van Heteren CF**, Nijhuis JG, Semmekrot BA, *et al.* Risk for surviving twin after fetal death of co-twin in twin-twin transfusion syndrome. *Obstet Gynecol* 1998;**92**:215–19.
- 26 **Saito K**, Ohtsu Y, Amano K, *et al.* Perinatal outcome and management of single fetal death in twin pregnancy: a case series and review. *J Perinat Med* 1999;**27**:473–7.
- 27 **Northern Regional Health Authority Coordinating Group**. Perinatal mortality: a continuing collaborative regional survey. *BMJ* 1984;**288**:1717–20.
- 28 **Glinianaia SV**, Rankin J, Renwick M. Time trends in twin perinatal mortality in northern England, 1982–94. Northern Region Perinatal Mortality Survey Steering Group. *Twin Res* 1998;**1**:189–95.
- 29 **MacKeith R**, Mackenzie I, Polani P. Definition and classification of cerebral palsy. *Cerebral Palsy Bulletin* 1959;**5**:23–35.
- 30 **Bax M**. Terminology and classification of cerebral palsy. *Dev Med Child Neurol* 1964;**6**:295–7.
- 31 **Jarvis SN**, Holloway JS, Hey EN. Increase in cerebral palsy in normal birthweight babies. *Arch Dis Child* 1985;**60**:1113–21.
- 32 **Norusis MJ**. SPSS for Windows. Base System user's guide, release 6.0. Chicago: SPSS, 1993.
- 33 **Gardner MJ**, Altman DG. *Statistics with confidence*. London: British Medical Journal, 1989.
- 34 **Pharoah POD**. Cerebral palsy in the surviving twin associated with infant death of the co-twin. *Arch Dis Child Fetal Neonatal Ed* 2001;**84**:F111–16.
- 35 **Pharoah POD**. Anomalies occur in registrations of fetal deaths in multiple pregnancies. *BMJ* 1999;**319**:188.
- 36 **Stanley F**, Blair E, Alberman E. Pathways to cerebral palsy involving very preterm birth. In: Bax MCO, ed. *Cerebral palsies: epidemiology and causal pathways*. London: Mac Keith Press, 2000:60–82.
- 37 **Chiswick ML**. Commentary on current World Health Organization definitions used in perinatal statistics. *Br J Obstet Gynaecol* 1986;**93**:1236–8.
- 38 **Wood NS**, Marlow N, Costeloe K, *et al.* Neurologic and developmental disability after extremely preterm birth. *N Engl J Med* 2000;**343**:378–84.
- 39 **Badawi N**, Kurinczuk J, Keogh JM, *et al.* Intrapartum risk factors for newborn encephalopathy: the Western Australian case-control study. *BMJ* 1998;**317**:1554–8.
- 40 **Bakketeig LS**. Only a minor part of cerebral palsy cases begin in labour. *BMJ* 1999;**319**:1016–17.
- 41 **Landy HJ**, Weiner S, Corson SL, Batzer *et al.* The “vanishing twin”: ultrasonographic assessment of fetal disappearance in the first trimester. *Am J Obstet Gynecol* 1986;**155**:14–19.
- 42 **Pharoah POD**, Cooke RW. A hypothesis for the aetiology of spastic cerebral palsy: the vanishing twin. *Dev Med Child Neurol* 1997;**39**:292–6.

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