Papers

Birth order, gestational age, and risk of delivery related perinatal death in twins: retrospective cohort study

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Abstract

Objective To determine whether twins born second are at increased risk of perinatal death because of complications during labour and delivery.
Design Retrospective cohort study.
Setting Scotland, 1992 and 1997.
Participants All twin births at or after 24 weeks' gestation, excluding twin pairs in which either twin died before labour or delivery or died during or after labour and delivery because of congenital abnormality, non-immune hydrops, or twin to twin transfusion syndrome.
Main outcome measure Delivery related perinatal deaths (deaths during labour or the neonatal period).
Results Overall, delivery related perinatal deaths were recorded for 23 first twins only and 23 second twins only of 1438 twin pairs born before 36 weeks (preterm) by means other than planned caesarean section ($P > 0.99$). No deaths of first twins and nine deaths of second twins ($P=0.004$) were recorded among the 2436 twin pairs born at or after 36 weeks (term). Discordance between first and second twins differed significantly in preterm and term births ($P=0.007$). Seven of nine deaths of second twins at term were due to anoxia during the birth (2.9 (95% confidence interval 1.2 to 5.9) per 1000); five of these deaths were associated with mechanical problems with the second delivery following vaginal delivery of the first twin. No deaths were recorded among 454 second twins delivered at term by planned caesarean section.
Conclusions Second twins born at term are at higher risk than first twins of death due to complications of delivery. Previous studies may not have shown an increased risk because of inadequate categorisation of deaths, lack of statistical power, inappropriate analyses, and pooling of data about preterm births and term births.

Introduction

Obstetricians recognise that second twins are vulnerable to complications during labour and delivery.[1] It is not clear, however, whether this is reflected in increased rates of perinatal mortality. Analysis of observational studies in the 1960s seemed to show that second twins were at higher risk of perinatal death than first twins.[2] These findings were subsequently refuted by a number of large scale studies that failed to show a higher risk[3–6] or that showed only a very slightly higher risk.[7] Previous large scale studies have generally lacked detailed information on the cause and timing of perinatal death. Consequently, differences in outcomes related to complications during delivery of the second twin may have been masked by other causes of death, such as prematurity, congenital abnormality, and antepartum events. We conducted a large scale, retrospective cohort study of delivery related perinatal deaths in twin pregnancies by linking a national register of data on discharges after childbirth to a national register of perinatal deaths.

Methods

Population

The Scottish morbidity record collects information on clinical and demographic characteristics and outcomes for all patients admitted to Scottish maternity hospitals. The register is subject to regular quality assurance checks, and data are available for more than 99% of registered births.[8] We used the register to identify all births between 1992 and 1997 and linked these records to records from the Scottish Stillbirth and Infant Death Enquiry, which has routinely classified all perinatal deaths in Scotland since 1983. It is virtually 100% complete and has been described in detail elsewhere.[9 10] The study used publicly collected data collected by NHS Scotland without identifiers and its use, therefore, did not require ethical approval.

Classification of perinatal deaths

Stillbirths were defined as babies born at or after 24 weeks' gestation who showed no signs of life after delivery. Stillbirths were subdivided into antepartum deaths (before the onset of labour) and intrapartum deaths (during labour). Neonatal death was defined as death during the first four weeks of life in a liveborn baby. The Scottish Stillbirth and Infant Death Enquiry's register documents the cause of death in two fields. Firstly, all deaths are classified according to a modified version of the Wigglesworth hierarchical system, which lists obstetric and paediatric causes[11]; the specific categories are described in detail elsewhere.[10] Secondly, each record has up to three obstetric and three paediatric ICD-9 (International Classification of Diseases, ninth revision) codes.

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bmj.com 2002;325:1004

We excluded all deaths that were due to congenital abnormality (Scottish Stillbirth and Infant Death Enquiry classifications 1-7), non-immune hydrops (ICD-9 code 778.0), and twin to twin transfusion syndrome (ICD-9 code 762.3). We defined delivery related perinatal death as intrapartum stillbirth or neonatal death not caused by congenital anomaly, hydrops, or twin to twin transfusion syndrome. The cause of death was subdivided into three paediatric categories: intrapartum anoxia, pulmonary causes, and all other paediatric causes. Within the category of intrapartum anoxia, we used the obstetric classification to identify deaths for which there was a direct obstetric mechanical cause, such as uterine rupture, malpresentation, cord compression (including prolapse), birth trauma, or anoxia associated with disproportion.

Definitions

Socioeconomic deprivation, smoking, parity, maternal age, and gestational age were defined as described previously.[12] Term was defined as ≥36 weeks' gestation for twin pregnancies.[6]

Statistical analyses

Continuous variables were summarised by the median and the interquartile range. Paired continuous data were compared by using the Wilcoxon signed rank test, and unpaired continuous data were compared by using the Mann-Whitney U test. Discordance in birth weight was described by the absolute difference, expressed as a percentage of the weight of the larger twin. Univariate comparisons of unpaired dichotomous data were performed using Fisher's exact test, χ^2 test, and χ^2 test for trend, as appropriate, and multivariate comparison was made using logistic regression. Univariate comparison of dichotomous outcomes in first and second twins was performed using the McNemar test, and multivariate comparison was performed by using conditional logistic regression. Socioeconomic deprivation, smoking, parity, height, and maternal age were categorised as in table 1 and were entered into the logistic regression model as a series of dummy variables. In each case the referent category is identified in the table. The P values for all hypothesis tests were two sided. The 95% confidence intervals for risk of death were calculated using the binomial distribution. All statistical analyses were performed using version 7.0 of the Stata software package.

Results

Between 1992 and 1997, 4707 women delivered twins in Scotland. Gestational age was missing in the records for two of these women (<0.1%). Of the remaining women, 4690 (99.7%) gave birth at or after 24 weeks' gestation. Records were excluded when one or both twins died from antepartum stillbirth (n=117), congenital abnormality (n=26), twin to twin transfusion syndrome (n=19), or non-immune hydrops (n=6). As some overlap existed between these groups, a total of 145 (3.1%) pregnancies were excluded. Among the

Table 1 Maternal characteristics in relation to preterm birth among 3874 women with twin pregnancies delivered by a means other than planned caesarean section. Values are numbers (percentages) unless otherwise specified

	Gestational age at delivery		Odds ratio (95% CI) for delivery at <36 weeks			
Characteristics	**<36 weeks (n=1438)**	**≥36 weeks (n=2436)**	**Unadjusted**	**P value***	**Adjusted**	**P value†**
Age:						
<20	63 (4.4)	70 (2.9)	1.0		1.0	
20-24	234 (16.3)	328 (13.5)	0.8 (0.5 to 1.2)		1.2 (0.8 to 1.9)	
25-29	487 (33.9)	814 (33.4)	0.7 (0.5 to 1.0)	0.0008	1.1 (0.7 to 1.8)	0.74
30-34	449 (31.2)	858 (35.2)	0.6 (0.4 to 0.8)		1.2 (0.7 to 1.8)	
>34	205 (14.3)	366 (15.0)	0.6 (0.4 to 0.9)		1.3 (0.8 to 2.1)	
Parity:						
0	754 (52.4)	904 (37.1)	1.0		1.0	
1	387 (26.9)	904 (37.1)	0.5 (0.4 to 0.6)	<0.0001	0.5 (0.4 to 0.6)	<0.0001
>1	297 (20.6)	628 (25.8)	0.6 (0.5 to 0.7)		0.5 (0.4 to 0.7)	
Smoking status:						
Non-smoker	686 (57.1)	1304 (60.3)	1.0		1.0	
Ex-smoker	114 (9.5)	198 (9.1)	1.1 (0.9 to 1.4)	0.07	1.0 (0.8 to 1.3)	0.09
Smoker	402 (33.4)	662 (30.6)	1.2 (1.0 to 1.3)		1.2 (1.0 to 1.4)	
Missing	236	272				
Deprivation category:						
1 (least deprived)	272 (19.3)	527 (22.0)	1.0		1.0	
2	250 (17.7)	495 (20.7)	1.0 (0.8 to 1.2)		1.0 (0.8 to 1.3)	
3	272 (19.3)	452 (18.9)	1.2 (1.0 to 1.4)	0.0005	1.1 (0.9 to 1.4)	0.26
4	309 (21.9)	478 (20.0)	1.3 (1.0 to 1.5)		1.2 (0.9 to 1.5)	
5 (most deprived)	305 (21.6)	443 (18.5)	1.3 (1.1 to 1.6)		1.3 (1.0 to 1.6)	
Missing	28	41				
Height (cm):						
<155	121 (10.1)	195 (8.8)	1.0		1.0	
155-159	264 (22.0)	399 (18.0)	1.1 (0.8 to 1.4)		1.1 (0.8 to 1.5)	
160-164	374 (31.2)	686 (31.0)	0.9 (0.7 to 1.1)	0.0005	0.9 (0.7 to 1.2)	0.002
165-169	277 (23.1)	564 (25.5)	0.8 (0.6 to 1.0)		0.8 (0.6 to 1.0)	
>170	164 (13.7)	367 (16.6)	0.7 (0.5 to 1.0)		0.7 (0.5 to 1.0)	
Missing	238	225				

*χ^2 test for trend.
†Likelihood ratio test.

Table 2 Delivery related perinatal deaths of first and second twins delivered by a means other than planned caesarean section in relation to gestational age and cause of death

Cause of death	Preterm births (n=1438)*: First twin	Second twin	Both twins	P value†	Odds ratio (95% CI) for second twin	Term births (n=2436): First twin	Second twin‡	Both twins	P value†	P value for preterm v term§
All	23	23	42	>0.99	1.0 (0.6 to 1.8)	0	9	0	0.004	0.007
Intrapartum anoxia	5	5	2	>0.99	1.0 (0.3 to 3.5)	0	7	0	0.02	0.04
Pulmonary causes	18	19	25	>0.99	1.1 (0.6 to 2.0)	0	0	0		
All other paediatric causes	11	10	4	>0.99	0.9 (0.4 to 2.1)	0	2	0	0.5	0.48

*In 11 of the preterm births, both twins died but because of different causes.
†McNemar's exact test for discordance between first twins and second twins.
‡Odds ratio for death of the second twin could not be calculated because the odds of death among first twins at term were zero in all categories.
§Fisher's exact test of discordant twin pairs, preterm versus term.

remaining 4545 pregnancies, 671 (14.8%) were delivered by planned caesarean section and 3874 (85.2%) by other means. On univariate analysis, age, socioeconomic status, height, and parity varied according to gestational age at the time of delivery in the group that excluded planned caesarean deliveries, but only parity and maternal height were independent predictors of preterm birth (table 1).

The numbers of deaths of first and second twins born before 36 weeks' gestation did not differ significantly (table 2). Among births at or after 36 weeks' gestation, no deaths were recorded among first twins and nine deaths among second twins (3.7 (95% confidence interval 1.7 to 7.0) per 1000 deliveries; P=0.004 for excess of deaths of second twins). Discordance between first and second twins was significantly different in preterm and term births (P=0.007; table 2).

Of the nine deaths of second twins at term, five were intrapartum stillbirths and four were neonatal deaths. Seven of the nine deaths were attributed to intrapartum anoxia (2.9 (1.2 to 5.9) per 1000 deliveries). Analysis of deaths due to intrapartum anoxia showed no difference between first and second twins born preterm (P > 0.99), a significant difference between first and second twins born at term (P=0.02), and a significant difference in the discordance between first and second twins for preterm and term births (P=0.04). The cause of death was classified as mechanical in five of the seven anoxic deaths at term; this equated to 2.1 (0.7 to 4.8) per 1000 deliveries. Both twins were delivered vaginally in six out of the seven deliveries at term in which the second twin died from anoxia and in all five of the deliveries at term in which anoxia had an obstetric mechanical cause. Both twins were delivered by emergency caesarean section in one case in which the second twin died from intrapartum anoxia. Among the 2427 term pregnancies for which both twins were delivered by a means other than planned caesarean section and for which neither twin died, 581 (23.9%) emergency caesarean sections were done for one or both twins.

No differences in any maternal characteristics for twins delivered at term by a means other than planned caesarean section were seen according to whether the second twin died (table 3). When twins' characteristics were compared, no difference was seen in the proportion that were discordant for sex, but the percentage discrepancy in birth weight was significantly higher for pairs of twins in which the second twin died than for pairs in which both twins survived (15.1% *v* 9.5%; P=0.02). When the actual weights for the nine pregnancies in which the second twin died during delivery at term were analysed, four of the second twins were larger than the first twins and five were smaller; the median birth weight did not differ between the first and second twins (2590 (interquartile range 2410-3060) g *v* (2400 (2268-2840) g; P=0.55).

When the risk of death for deliveries from 24 weeks onwards by a means other than planned caesarean section was analysed with conditional logistic regression, a significant interaction between birth order and gestational age was confirmed: the odds ratio for the interaction term between gestational age, expressed as a continuous variable in weeks, and the second twin was 1.16 (1.01 to 1.35; P=0.04). No significant interactions were seen between second twin and maternal age, parity, height, smoking, or deprivation category (all P > 0.05). In a model that included all of these interaction terms, the interaction between second twin and gestational age was significant (odds ratio 1.36, 1.01 to 1.85; P=0.04).

When outcomes for the 454 twin pairs delivered at term by planned caesarean section were analysed, no delivery related perinatal deaths of either first or

Table 3 Maternal and obstetric characteristics of pregnancies at term according to death of second twin among women not delivered by planned caesarean section. Values are numbers (%) unless otherwise specified

Characteristics	Both twins survived (n=2427)	Second twin died (n=9)	P value*
Mother			
Median (interquartile range) maternal age (years)	30 (26-33)	29 (26-32)	0.99
Median (interquartile range) height (cm)	163 (159-167)	162 (158-165)	0.72
Nulliparous	900 (37.1)†	4 (44.4)	0.73
Smoker	660 (30.6)†	2 (22.2)	>0.99
In upper two fifths of deprivation category	1000 (41.9)†	5 (55.6)	0.50
Twin			
Discordant for sex	808 (34.0)	2 (22.2)	0.73
Median (interquartile range) % discrepancy in birth weight	9.5 (4.5-15.9)	15.1 (12.1-21.0)	0.02

*Percentage estimated after records with missing values were excluded.
†Fisher's exact test or Mann Whitney U test, as appropriate.

second twins were seen. Among women who gave birth at term, deaths of second twins delivered by planned caesarean section and those delivered by other means did not differ significantly (P=0.22, Fisher's exact test).

Discussion

We observed an excess of delivery related perinatal deaths of second twins born at term compared with their cotwins. No difference in outcome was seen between first and second twins born preterm. The absolute risk of perinatal death for second twins born at term was approximately 1 in 270 for all causes, 1 in 350 for death due to intrapartum anoxia, and 1 in 500 for anoxic death due to a mechanical cause. These absolute risks are high in comparison with singleton births in Scotland over the same period: for singleton pregnancies at term delivered by a means other than planned caesarean section, delivery related perinatal death occurred in about 1 in 1000 births among nulliparous women and 1 in 2000 births among multiparous women; death due to a mechanical obstetric cause occurred in only 1 in 20 000 births.[13]

Methodological issues

Many studies have examined the issue of delivery related mortality in second twins. These studies have compared the outcome of second twins born vaginally either with vaginally delivered cotwins[2 3 5–7] or with second twins delivered by caesarean section.[4 14–16] They failed to show a significant association between birth order and the risk of delivery related perinatal death. We were able to make both comparisons in our study and also addressed several limitations in methods that were apparent in previous studies.

Firstly, this study examined the outcomes of over 4500 twin pairs. Many previous studies that examined perinatal mortality in relation to birth order had fewer than 1000 twin pairs and many had fewer than 500 twin pairs (see Boggess [17] for review). Given the relative rarity of delivery related perinatal death caused by intrapartum anoxia,[13] such studies are clearly underpowered and would inevitably yield negative findings.

Secondly, to our knowledge, this study is the only large scale analysis to include data on both intrapartum stillbirths and neonatal deaths but to exclude antepartum deaths. Given that most delivery related perinatal deaths in second twins at term were intrapartum stillbirths, previous large scale studies that excluded stillbirths probably underestimated the risk to the second twin.[3–5 7] The only large scale study that included stillbirths was unable to distinguish between antepartum and intrapartum stillbirths.[6]

Thirdly, most studies have compared first and second twins across the whole range of gestational ages rather than stratified by gestational age.[3 5 7] The former method is legitimate only if the relative risk is homogeneous across the range of gestational ages. A statistical interaction between birth order and gestational age, however, is predictable. Eighty per cent of twins delivered at 24 weeks die compared with less than 1% at term.[6] The principal determinant of the risk of death is prematurity, which clearly is the same for both twins. The potential for birth order to increase the baseline risk due to complications during labour and delivery, therefore, would be expected to increase with advancing gestational age. Our study confirmed a positive interaction between being a second twin and gestational age and thus confirms that the assumption of homogeneity implicit in previous analyses was invalid. Other maternal factors were also associated with preterm birth (table 1). Multivariate conditional logistic regression showed that the interaction between gestational age and birth order was not explained by an interaction between birth order and any of the other factors.

Finally, our statistical analysis took into account the paired nature of the data. Many previous studies, including previous large scale analyses,[3–7] compared data on first and second twins by using statistical techniques that assume independence of observations. The use of unpaired tests for paired data is inappropriate and results in loss of statistical power. We overcame this using McNemar's test and conditional logistic regression. If we had used the same analytical approach as some previous studies (failed to stratify by gestational age and used a statistical test for unpaired data), we would have observed, overall, 67 deaths among all first twins and 75 among second twins; this would have failed to reach significance (χ^2 test, P=0.49).

The excess of deaths due to intrapartum anoxia was significant only for twins born at term (table 2). Although no significant difference was seen between the risks of death for first and second twins born preterm, the confidence intervals for the odds ratio of death of the preterm second twin (relative to the first twin) due to intrapartum anoxia were 0.3 to 3.5. Our data cannot exclude an excess risk of anoxic death for preterm second twins; further larger analyses are required.

Discordance

No maternal characteristics were associated with an increased risk of delivery related perinatal death for second twins delivered at term (table 3). The absolute discrepancy in weight between twins was greater, however, in pregnancies complicated by death of the second twin at term. Interestingly, the discrepancies were equally distributed between pregnancies in which the second twin was larger than the first and those in which the first twin was larger. The actual number of events was too small to establish the relation between the direction of the weight difference and the cause of death. The registers we used lacked information on the presentation of the second twin before delivery of the first. However, the presentation of the second twin changes after delivery of the first twin in 20% of cases,[1] so it may not be possible to predict, before the first twin is delivered, which cases will be complicated by malpresentation of the second twin.

Caesarean deliveries

Since the excess of deaths of second twins at term seems to be attributable to labour, current data suggest that planned caesarean delivery may be protective against perinatal death among twins. Though no deaths occurred among 454 second twins delivered by planned caesarean section at term, the numbers were too small to confirm a protective effect of planned caesarean section. Previous studies on the association between caesarean section and the risk of perinatal death among second twins included fewer cases than reported in this study[14–16] or lacked information on

What is already known on this topic

It is difficult to assess the wellbeing of second twins during labour

Deliveries of second twins are at increased risk of mechanical problems, such as cord prolapse and malpresentation, after vaginal delivery of first twins

Increased risks of perinatal death in second twins have not been shown, but the methods of these studies were flawed

What this study adds

Second twins delivered at term are at increased risk of delivery related perinatal deaths

Intrapartum anoxia caused 75% of these deaths in second twins, and most of these resulted from mechanical problems after vaginal delivery of first twins

Planned caesarean section of twins at term may prevent perinatal deaths

whether the procedure was planned or an emergency procedure.[4] Sample size calculations show that it will be difficult to obtain randomised controlled trial data to test the hypothesis that planned caesarean section would be protective against perinatal death in twin pregnancies. With a rate of three deaths of second twins due to intrapartum anoxia per 1000 deliveries, allowing 80% power for a one sided test, and assuming that the rate of perinatal death in the planned caesarean group is zero, a randomised controlled trial would need to recruit about 6500 women with twin pregnancies. We propose that women with twins should be counselled about the risk to the second twin and the theoretical possibility of a protective effect of planned caesarean section when considering mode of delivery at term.

We thank Ian White, a senior scientist at the Medical Research Council Biostatistics Unit, Cambridge, for helpful discussion regarding the statistical analysis and for reviewing the completed manuscript.

Contributors: GS had the original concept, reviewed previous publications, undertook the statistical analyses, and wrote the initial draft. RD performed the record linkage. GS, JP, and RD agreed the study design, interpreted the results, revised the original draft, and approved the final version. GS is the guarantor.

Funding: No external funding.

Competing interests: None declared.

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(Accepted 6 June 2002)