

Birth order of twins and risk of perinatal death related to delivery in England, Northern Ireland, and Wales, 1994-2003: retrospective cohort study

Gordon C S Smith,¹ Kate M Fleming,² Ian R White³

EDITORIAL by Steer

¹Department of Obstetrics and Gynaecology, Cambridge University, Box 223, The Rosie Hospital, Cambridge CB2 2QQ

²Confidential Enquiry into Maternal and Child Health, London NW1 5SD

³Medical Research Council Biostatistics Unit, Institute of Public Health, Cambridge CB2 2SR

Correspondence to: G C S Smith
gcss2@cam.ac.uk

BMJ 2007;334:576-8

doi: 10.1136/bmj.39118.483819.55

ABSTRACT

Objective To determine the effect of birth order on the risk of perinatal death in twin pregnancies.

Design Retrospective cohort study.

Setting England, Northern Ireland, and Wales, 1994-2003.

Participants 1377 twin pregnancies with one intrapartum stillbirth or neonatal death from causes other than congenital abnormality and one surviving infant.

Main outcome measures The risk of perinatal death in the first and second twin estimated with conditional logistic regression.

Results There was no association between birth order and the risk of death overall (odds ratio 1.0, 95% confidence interval 0.9 to 1.1). However, there was a highly significant interaction with gestational age ($P<0.001$). There was no association between birth order and the risk of death among infants born before 36 weeks' gestation but there was an increased risk of death among second twins born at term (2.3, 1.7 to 3.2, $P<0.001$), which was stronger for deaths caused by intrapartum anoxia or trauma (3.4, 2.2 to 5.3). Among term births, there was a trend ($P=0.1$) towards a greater risk of the second twin dying from anoxia among those delivered vaginally (4.1, 1.8 to 9.5) compared with those delivered by caesarean section (1.8, 0.9 to 3.6).

Conclusions In this cohort, compared with first twins, second twins born at term were at increased risk of perinatal death related to delivery. Vaginally delivered second twins had a fourfold risk of death caused by intrapartum anoxia.

INTRODUCTION

Though vaginal delivery of a second twin is recognised as a time of obstetric risk, we do not know whether second twins are at increased risk of perinatal death. Many studies on the association between birth order and the risk of death have methodological flaws, specifically, the failure to identify deaths truly related to delivery, the failure to use paired statistical tests to compare the outcome of first and second twins, and the failure to stratify analyses by gestational age.¹ Two studies of perinatal death data from Scotland showed a significantly increased risk of intrapartum stillbirth or neonatal death among second twins born at term.^{2,3} A subsequent analysis of US data found no variation in the risk of neonatal death related to birth order among twins and concluded that the increased perinatal mortality among second twins was "merely an artefact of mortality comparisons."⁴ It remains unclear, therefore, whether attempted vaginal delivery of the second twin at term is associated with an increased risk of perinatal death. We studied the association between birth order and the risk of perinatal death among twin pregnancies in England, Northern Ireland, and Wales, 1994-2003.

METHODS

Data on perinatal death in England, Northern Ireland, and Wales have been collected nationally since 1994 and are currently coordinated by the Confidential Enquiry into Maternal and Child Health (CEMACH). We used the registry of deaths for 1994-2003 for our analyses.

We obtained the total number of twin births over the time period from the Office of National Statistics and the Northern Ireland Statistics and Research Agency. These statistics lack any detailed obstetric data. Our analyses were limited to the relative risk of death for the second twin referent to the first and determination of whether the relative risk of death for the second twin varies in relation to any characteristic common to both, such as gestational age and maternal characteristics.

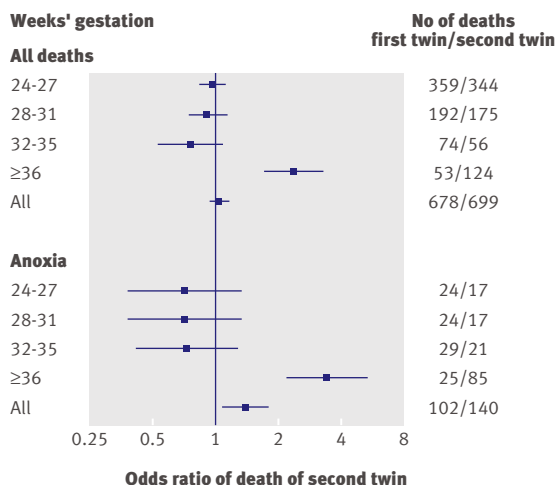
We excluded antepartum stillbirths and all deaths where the cause was stated to be a lethal or severe congenital abnormality. Intrapartum stillbirths and neonatal deaths unrelated to congenital abnormality were defined as perinatal deaths related to delivery. We also analysed the subgroup (anoxic deaths) where the cause was classified as "death from intrapartum asphyxia, anoxia, or trauma."

Statistics

We used conditional logistic regression to estimate the odds ratio of death for the second twin referent to the first. The method ignores concordant pairs (that is, where both twins survived or both twins died) and is therefore appropriate in a dataset containing data on deaths only. We tested for interactions between birth order and maternal characteristics and method of delivery.

RESULTS

The study group consisted of 1377 twin pregnancies in which there was one intrapartum stillbirth or neonatal death, unrelated to congenital abnormality but the other twin survived. Over the same period of time, there were 99 598 twin pregnancies. Birth order was not associated with the overall risk of perinatal death related to delivery: the odds ratio for the second twin was 1.0 (95% confidence interval 0.9 to 1.1). There were no significant interactions between birth order and maternal age. There was, however, a highly significant interaction with gestational age ($P<0.001$). There was no association between birth order and the risk of death among infants born before 36 weeks' gestation (figure), but there was an increased risk of death among second twins born at term (2.3, 1.7 to 3.2, $P<0.001$). When we confined the analysis to deaths caused by



Odds ratio for perinatal death related to delivery of second twin for all causes and deaths caused by anoxia, stratified by gestational age. Numbers of deaths are actual numbers of losses of first and second twins, confined to births where other twin survived.

anoxia, there was a weak association with being a second twin for all births (1.4, 1.1 to 1.8, $P=0.02$). Again, there was a highly significant interaction with gestational age ($P<0.001$). When we stratified by gestational age, we found no association between birth order and the risk of death caused by anoxia before 36 weeks (figure) but a strong association for births at and beyond 36 weeks (3.4, 2.2 to 5.3).

We then assessed the risk of perinatal death related to delivery among second twins born at term in relation to method of delivery in the 121 twin pairs for whom we had this information. When we looked at all causes of perinatal death related to delivery we found no significant difference in those delivered by caesarean section (odds ratio for interaction term 0.9, 0.4 to 1.8, $P=0.7$). When we confined the analysis to deaths caused by intrapartum anoxia we found an interaction of borderline significance between birth order and caesarean section (0.4, 0.1 to 1.3, $P=0.1$). The odds ratio for the second twin was 1.8 (0.9 to 3.6) among those delivered by caesarean section and 4.1 (1.8 to 9.5) among those delivered vaginally. There were only 19 twin pairs delivered by planned caesarean section at term where one died and the other survived. Among this group, the odds ratio for any perinatal death of the second twin related to delivery was 1.4 (0.6 to 3.4) and 1.0 (0.1 to 7.1) for death caused by anoxia.

DISCUSSION

In this retrospective cohort study we found an increased risk of death of second twins compared with first twins born at term in England, Northern Ireland, and Wales, 1994-2003. There was an interaction between the effect of birth order and gestational age. There was no association between birth order and the risk of death among infants born at preterm gestations, but we found a strong association between birth order and the risk of death at term. The interaction

between birth order and gestational age is unlikely to be a chance finding. Firstly, it was highly significant ($P<0.001$). Secondly, we had previously observed such an interaction in another population,² and the presence of an interaction was a prior hypothesis. Thirdly, it is biologically plausible. The risk of death at term is low and a small absolute risk of complications for the second twin will result in a much greater relative risk of death (when compared with the first twin) than at preterm gestations, where the background risk of death is high for both.² The association between birth order and the risk of perinatal death at term was stronger for deaths attributed to intrapartum anoxia. These findings clearly show an increased risk for death of the second twin delivered at term, principally because of complications of labour and delivery.

Comparison with other research

A previous observational study found a lower risk of death of either twin with planned caesarean delivery.³ Consistent with this, the risk of anoxic death of the second twin was lower among those delivered by caesarean section than those delivered vaginally, although not significantly so. The data source we used was confined to infants who died so we did not know how the surviving twin had been delivered. In some cases where the second twin died after a caesarean delivery, the first twin may have been delivered vaginally. This delivery combination is known to increase the risk of death for the second twin.^{5,6} It is likely, therefore, that the protective effect of caesarean delivery would be greater than our results suggest.

A large scale study of US birth and death certifications (1995-7) published in 2004 found no significant difference in the risk of neonatal death among second twins.⁴ The analysis, however, had several weaknesses—namely, the failure to use paired statistical comparison of first and second twins, the known shortcomings of the US birth and death certification databases,^{7,8} and stratification by birth weight rather than gestational age. Moreover, other analyses of the same data source suggested an increased risk of death of the second twin related to delivery: the risk of neonatal death of the second twin was lower where the twin pair was delivered by caesarean section compared with those delivered vaginally.^{5,6} The US data also lack information on whether death of the infant occurred before or during labour and cannot, therefore, address the effect of birth order on the risk of intrapartum stillbirth. The strengths of our study are the use of more appropriate statistical methods and that data were available for a large number of losses, including detailed information on both the timing and cause of perinatal death.

Our results are consistent with those of several previous studies of birth order and perinatal morbidity. These have shown an increased risk of a depressed five minute Apgar score in the second twin.^{9,10} We found no association between birth order and the risk of perinatal death at preterm gestations, whereas other studies have shown an increased risk of fetal distress or morbidity for second twins born preterm.¹⁰ Our

WHAT IS ALREADY KNOWN ON THIS TOPIC

Vaginal delivery of the second twin is recognised as a time of high risk

Recent studies of the effect of birth order on the risk of perinatal death have produced inconsistent results

WHAT THIS STUDY ADDS

There was no association between birth order and the relative risk of perinatal death related to delivery among preterm twins

At term, the second twin had a greater than twofold risk of perinatal death related to delivery and a greater than threefold risk of death caused by intrapartum anoxia

interpretation of these findings is that labour and delivery are associated with risks to the second twin at all gestations. The major determinant of perinatal death at preterm gestations, however, is the degree of prematurity. Hence, a small additional risk to the second twin during vaginal birth has no significant effect on the relative risk of death, except at term. The findings of this and other studies suggest that planned caesarean section may be beneficial for all twins. Direct evidence for a protective effect of caesarean section would require a randomised controlled trial, although statistical power might be a problem.² This and previous studies have important lessons for any randomised controlled trial of planned caesarean section for all twin pregnancies. Inclusion of preterm births may mask a protective effect of caesarean section on perinatal mortality if the principal effect of caesarean section is to reduce the risk of complica-

tions for the second twin. Moreover, this and previous studies showed that it is a minority of all perinatal deaths of twins that are related to complications during labour and delivery. Failure to exclude losses that are largely independent of method of delivery, including antepartum stillbirth and deaths caused by congenital abnormality or prematurity, may mask a protective effect of caesarean delivery.

Contributors: See bmj.com.

Funding: None.

Competing interests: None declared.

Ethical approval: The directors of CEMACH approved the study.

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Accepted: 18 January 2007

No effect

To indicate “no” speechlessly, you shake your head. You might add a grimace and perhaps a grunt, such as “a-a” or “n-n.” These sounds give us prefixes and words that mean “no.”

The Greek privative prefix “a-” (expressing negation) can be seen in words such as aplasia, asterixis, astigmatism, atresia, and (as “an-”) anaesthetic, anorexia, and carbonic anhydrase. The prefix also occurs in Sanskrit, as in the Indian girl’s name Amrita (literally “deathless”) from the gods’ drink of immortality (compare “ambrosia” in Greek).

In Latin the equivalent was “in-” and its variants (“il-,” “im-,” “ir-”), as in incontinent, illegitimate, immature, and that irritating phrase, irregularly irregular. In Teutonic languages it became “un-” (unbalanced, unstriated). Many negative Latin words, such as negare (to naysay), begin with an “n”—ne (lest, or so that not), nec or neque (nor), non (not), num (surely not?), nil and nihil (nothing), nullus and nemo (no one), neuter (neuter, not either), and nolle (to want not to, as in volens nolens, willy-nilly). Nepenthes, a Greek nickname for Apollo, gives us the opioid nepenthe (ne penthos = no sorrow).

Some surprising words have “no” in them. “Negotiate”

was Latin necque otium (no leisure), “necessary” is from ne cessum (not given up), and “nice” was originally from nescius (stupid, from nescire (to be ignorant), see *BMJ* 2000;320:749).

My impression that more pieces of negative work are being published in bioscience journals has been confirmed by a quick search of PubMed for papers whose titles contain the words “no effect.” From 1951 to 1970 there were 11. The 1951 example was in French, and the next, in 1958, was in English. Since then the number has been steadily increasing; in 2005 it was 91. This must be just the tip of the negative iceberg.

Journals and authors are certainly more willing to publish negative results nowadays. But are we perhaps also running out of scientific steam?

Jeff Aronson clinical pharmacologist, Oxford
jeffrey.aronson@clinpharm.ox.ac.uk

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