The epidemiology of sudden infant death syndrome

M J Platt, P O Pharoah

Background: Twins compared to singletons are at increased risk of sudden infant death syndrome (SIDS).

Aims: To compare the epidemiology of SIDS in twins and singletons and to test the hypothesis that monozygous (MZ) were at greater risk of SIDS than dizygous (DZ) twins.

Methods: Data from the Office for National Statistics on all registered live births and infant deaths with registered cause of death “sudden unexpected death in infancy” in England and Wales from 1993 to 1998 were obtained, together with the registered birth weight and, for twins, whether they were of like or unlike sex.

Results: The crude relative risk of SIDS in twins is twice that in singletons. There has been a significant temporal decline in SIDS mortality. There is also a significant increase in risk with decreasing birth weight for both twins and singletons. The birth weight specific risk of SIDS in all except for those >3000 g is greater in singletons than in twins. There is no significant difference in risk of SIDS in like compared with unlike sex twins.

Conclusions: In spite of a lower risk of SIDS in twins compared with singletons for each birth weight group <3000 g, one component of the higher crude relative risk of SIDS in twins is attributable to the higher proportion of twins that are of low birth weight. A second component is the higher risk in twins compared with singletons for those of birth weight ≥3000 g. Like sex are at no greater risk than unlike sex twins, which suggests that zygosity is not a significant factor in SIDS.

The epidemiology of SIDS shows a two- to fourfold increased risk for twins compared with singletons. Some of the excess risk may be attributable to confounding by birth weight, but there are conflicting reports of whether or not any increased risk of SIDS is independent of birth weight. An early study of SIDS found that twins of birthweight groups ≤2000 g and 2001–2500 g were at significantly increased risk compared with singletons, and concluded that the increased risk among twins is independent of birth weight. In contrast, a more recent study concluded that, independent of birth weight, twins do not appear to be at greater risk for SIDS compared with singleton births. In any assessment of the birthweight effect on SIDS mortality in twins, zygosity must also be taken into consideration. The lower the birth weight, the greater is the likelihood that the twins are monozygous (MZ); and MZ are at greater risk than dizygous (DZ) twins of fetal and infant death, cerebral impairment, and other congenital anomalies.

The aims of the study were: to compare trends in mortality as a result of SIDS in singleton and multiple births; and to test the hypothesis that MZ would be at greater risk than DZ twins of SIDS, and that the epidemiology of SIDS would differ in MZ and DZ twins.

METHODS

National birth and death registrations for England and Wales, 1993–98, provided denominator data. All deaths with an underlying cause of death certified as “sudden death, cause unknown”, International Classification of Disease, 9th revision (ICD) three digit code number 798 were included.

Total numbers of live births and cases of SIDS in birthweight specific groups were obtained from routinely published national statistics. Birthweight groups used for the analyses were <1500 g, 1500–2499 g, 2500–2999 g, 3000–3499 g, ≥3500 g, and “birth weight not stated”.

The ONS provided copies of the non-confidential section of all death registrations in twins and higher order multiple births in England and Wales 1993–98 with coding of the causes of death. The death registrations also provided information on the age at death, birth weight, and whether twins were of like or unlike sex. National birth and death registrations do not allow twins to be classified as MZ or DZ, only as of like or unlike sex. As unlike sex twins must be DZ but like sex twins comprise both DZ and MZ twins, the risk of like and unlike sex twins was compared. ONS also provided data on the registered birth weight of the surviving co-twin. Denominator numbers of twins of like and unlike sex were obtained from routinely published annual registrations.

The number of SIDS in singletons was obtained by subtracting the number of SIDS in multiple births from the total number of SIDS. The annual numbers shown relate to the year of birth, not year of death. For example, an infant born in 1993, who dies in 1994 will be included in the numerator SIDS for 1993. Similarly, infants born in 1998 but who died with SIDS in 1999 were included in the numerator for 1998. Deaths owing to SIDS that occurred after 1 year of age were excluded from the analyses.

Statistics

The difference between two independent proportions was examined by a χ² test. Trends were examined using χ² for trend. “EpiInfo 2000 was used to determine the birthweight specific and crude relative risks, and the Mantel-Haenszel weighted relative risk.

RESULTS

There were 2349 SIDS cases among infants born from 1993 to 98; of these deaths, 2248 occurred in infancy—that is, aged less than 1 year. The remaining 101 (96 singletons and five

Abbreviations: DZ, dizygous; MZ, monozygous; ONS, Office for National Statistics; SIDS, sudden infant death syndrome

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twins) SIDS occurred when the children were aged 1–4 years and were excluded from the analyses.

**Annual trend in SIDS mortality in singletons and twins**

Table 1 shows the annual trend in mortality as a result of SIDS. Over the six year study period, the crude SIDS mortality per 1000 livebirths was 1.13 in twins and 0.56 in singletons; the relative risk of twins compared with singletons was 2.02 (95% CI 1.67 to 2.43; p < 0.0001). The downward trend in annual SIDS mortality was significant for both singletons ($\chi^2$ for trend p < 0.0001) and twins ($\chi^2$ for trend p < 0.02).

**Birthweight specific SIDS mortality in singletons and twins**

Table 2 shows the birthweight specific SIDS mortality in twins and singletons. Among singletons, there is a striking increase in SIDS mortality with decreasing birthweight ($\chi^2$ for trend p < 0.0001). Among twins the inverse association of birth weight and SIDS mortality is seen only in the three lowest birth weight groups, <1500 g, 1500–2499 g, and 2500–2999 g. In all three birth weight groups, the relative risk of SIDS is lower in twins than in singletons. In contrast, among infants of birth weight $\geq$3000 g, the relative risk in twins is significantly greater than in singletons (Mantel-Haenszel weighted relative risk in 2 strata (3000–3499 g and $\geq$3500 g) = 2.83; 95% CI 1.72 to 4.63; p < 0.0001). There are, therefore, two components to the higher crude SIDS mortality in twins compared with singletons. These are the greater proportion of low birthweight infants among twins in whom SIDS mortality is high, and the higher SIDS mortality in twins of birth weight $\geq$3000 g. For example, in table 2 it can be shown that 65% of twin SIDS but only 21% of singleton SIDS are of low birth weight (<2500 g).

**Birthweight specific SIDS mortality in like and unlike sex twins**

As MZ twins are at increased risk of dying in infancy compared with DZ twins, it was hypothesised that some of the increased risk may be attributable to SIDS. There were no significant birthweight specific differences in risk of SIDS in like compared with unlike sex twins (table 3). Among twins of like sex, the surviving twin was likely to be of greater birth weight than the co-twin who died with SIDS. In contrast, among unlike sex twins, the child dying with SIDS was likely to be of greater birth weight (table 4).

**DISCUSSION**

The first official definition of SIDS was “the sudden death of any infant or young child which is unexpected by history and in whom a thorough necropsy examination fails to show an

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Table 1: Trends in mortality due to SIDS

<table>
<thead>
<tr>
<th>Year</th>
<th>Singletons</th>
<th>Twins</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>407</td>
<td>23</td>
<td>2132</td>
</tr>
<tr>
<td>1994</td>
<td>397</td>
<td>20</td>
<td>2017</td>
</tr>
<tr>
<td>1995</td>
<td>344</td>
<td>25</td>
<td>2019</td>
</tr>
<tr>
<td>1996</td>
<td>371</td>
<td>21</td>
<td>2266</td>
</tr>
<tr>
<td>1997</td>
<td>353</td>
<td>15</td>
<td>2068</td>
</tr>
<tr>
<td>1998</td>
<td>260</td>
<td>11</td>
<td>2071</td>
</tr>
<tr>
<td>Total</td>
<td>2132</td>
<td>115</td>
<td>2247</td>
</tr>
</tbody>
</table>

Table 2: Birthweight specific SIDS mortality rates in singletons and twins

<table>
<thead>
<tr>
<th>Birthweight group</th>
<th>Singletons</th>
<th>Twins</th>
<th>Twin/Singleton relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1500 g</td>
<td>76</td>
<td>16</td>
<td>0.81 (0.47 to 1.38) NS</td>
</tr>
<tr>
<td>1500–2499 g</td>
<td>371</td>
<td>59</td>
<td>1.36 (0.54 to 1.23) NS</td>
</tr>
<tr>
<td>2500–2999 g</td>
<td>537</td>
<td>24</td>
<td>0.72 (0.54 to 0.90) p&lt;0.01</td>
</tr>
<tr>
<td>3000–3499 g</td>
<td>657</td>
<td>15</td>
<td>2.98 (1.79 to 4.97) p&lt;0.0001</td>
</tr>
<tr>
<td>$\geq$3500 g</td>
<td>456</td>
<td>1</td>
<td>6.11 (0.23 to 11.45) NS</td>
</tr>
<tr>
<td>Not stated</td>
<td>35</td>
<td>0</td>
<td>2.12 (1.75 to 2.55) p&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 3: Birthweight specific SIDS mortality rates in like and unlike sex pairs

<table>
<thead>
<tr>
<th>Birthweight group</th>
<th>Like sex</th>
<th>Unlike sex</th>
<th>Relative risk like/unlike sex (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1500 g</td>
<td>15</td>
<td>1</td>
<td>5.93 (0.78 to 44.89) NS</td>
</tr>
<tr>
<td>1500–2499 g</td>
<td>40</td>
<td>19</td>
<td>0.97 (0.56 to 1.67) NS</td>
</tr>
<tr>
<td>2500–2999 g</td>
<td>15</td>
<td>9</td>
<td>0.88 (0.39 to 2.02) NS</td>
</tr>
<tr>
<td>$\geq$3000 g</td>
<td>7</td>
<td>9</td>
<td>0.38 (0.14 to 1.03) NS</td>
</tr>
<tr>
<td>All</td>
<td>77</td>
<td>38</td>
<td>1.16 (0.78 to 1.78) NS</td>
</tr>
</tbody>
</table>

*Includes 948 birth weight not stated.
†Includes 444 birth weight not stated.
‡Mantel-Haenszel weighted relative risk.
adequate cause of death". This definition means that a diagnosis of SIDS is one made by exclusion, and the thoroughness of the postmortem examination may be crucial to eliminating a recognisable adequate cause of death. In England and Wales, it was not until 1971 that "sudden death, cause unknown" was accepted as a natural registrable cause of death by the Registrar General. This acceptance of SIDS as a registrable entity led, in the decade of the 1970s, to an increase in numbers so registered which was largely an artefact owing to transference from respiratory causes of death. There has been a continuous downward trend in SIDS mortality following the earlier artefactual rise. The trend was intensified following the national "back to sleep" campaign in 1991, and we have now shown that SIDS mortality continues to fall significantly in both singletons and twins in the period 1993–98. The thoroughness of postmortem examination is likely to vary throughout the country. As the study is based on nationally registered SIDS, it could be inferred that the downward trend was, in part, an artefact of the improvement in the quality of postmortem examination, thereby reducing the number of deaths by exclusion. Any improvement in the thoroughness of postmortem examination may be counteracted by the falling numbers of postmortem examinations. However, the decline in SIDS mortality has been of such magnitude that to make this an unlikely explanation; the alternate explanation of a real improvement is more probable.

An objective of the study was to test the hypothesis that zygosity may influence the risk of death as a result of SIDS. The failure to observe any effect of zygosity must be interpreted with caution because like or unlike sex of twins is only a partial marker of zygosity. All unlike sex twins are dizygous, but only about 50% of like sex twins are monzygous.

Several studies have found that twins have a two- to fourfold increased risk of SIDS compared with singletons. There are at least two components to this increased risk. Premature delivery and low birth weight is associated with increased rates of SIDS, and a much higher proportion of twins compared with singletons are born preterm or of low birth weight. Birth weight specific twin/singleton comparisons of risk have produced conflicting results. The 1968 Californian live birth cohort study found a higher risk in twins for all three birthweight specific groups (<2000 g, 2001–2500 g, and >2500 g) examined. A more recent United States national study found a higher, but not statistically significant, SIDS risk in singletons compared with twins for the birth weight groups 500–1499 g and 1500–2499 g, but a lower risk for the birth weight group >2500 g. Our results are in accord with the United States study. A possible explanation is that birth weight is a marker for gestational age and, for a given birth weight group, twins are gestationally more mature than twins. The mechanism whereby gestational maturity exerts an influence may be through the immunocompetence of the developing fetus. A newborn’s ability to produce IgG is low, and transplacental transfer of maternal IgG during the second and third trimesters is the basis of passive protection in early neonatal life and could influence the probability of the infant succumbing to SIDS. This presupposes that some SIDS deaths have an infectious aetiology.

Our observation that heavier twins (birth weight ≥3000 g) are at greater risk of SIDS than singletons is unusual and has not been reported previously. Within a population preventive perspective of SIDS mortality, the attributable risk associated with large twins is small because they are relatively few of them. However, the high relative risk may be of aetiological significance. It seems unlikely that immunological competence is important in these cases. Possible factors such as maternal diabetes and the greater propensity of large twins to suffer perinatal injury are conjectural. The question of why large twins are at high risk is intriguing. However, the increased risk of SIDS in twins of birth weight ≥3000 g is based on only 16 observed cases when 5.5 were expected. Nevertheless, this is unlikely to be a result of chance and merits specific confidential enquiry into individual cases.

ACKNOWLEDGEMENTS

The authors wish to thank Nirupa Dattani and Beverley Botting of ONS for supplying the registration data and the Foundation for the Study of Infant Death for funding the study.

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REFERENCES


Table 4

<table>
<thead>
<tr>
<th>Birthweight differences between SIDS and co-twin</th>
<th>Like sex twins*</th>
<th>Unlike sex twins†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight of SIDS child greater than the co-twin survivor</td>
<td>28</td>
<td>20</td>
</tr>
<tr>
<td>Birth weight of SIDS child less than the co-twin survivor</td>
<td>45</td>
<td>17</td>
</tr>
</tbody>
</table>

χ² (with Yates’s correction): df = 1.8; NS.

*In four cases birth weights of both twins were the same.
†In one case birth weights of both twins were the same.