Fetal and infant death in mono- and dizygotic twins in England and Wales 1982–91

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Abstract

Aim—To quantify the level of risk for stillbirth and infant death in singleton compared with twin pregnancies, using national data; to determine the independent effects of zygosity, sex, and birthweight on these risks in twin pregnancies.

Methods—A retrospective national study was carried out of all singleton and twin birth and death registrations in England and Wales 1982–91, according to sex and birthweight group. Weinberg's rule was applied to the twin pairs to differentiate mono- from dizygotic twins. Relative risks for mono- compared with dizygous twins for both twins being stillbirths and for one of the pair being a stillbirth were determined. For twins where one was stillborn and the other live born, the relative risk of neonatal and infant mortality in the surviving co-twin was determined.

Results—There were 6 563 834 registered singletons and 70772 registered twin pairs for the period under study. Monozygotic twins had a relative risk of: 18.91 (95% CI 12.48–28.64) for both twins being stillborn; 1.63 (95% CI 1.48–1.79) for one twin being a stillbirth; and 2.26 (95% CI 1.45–3.52) for the live born co-twin dying as a neonate. When both twins were live born and among singletons, the odds ratio for neonatal mortality of being male was 1.41 (95% CI 1.37–1.45) and there was a highly significant negative association with birthweight. After adjusting for birthweight group and sex, twins had a reduced neonatal mortality compared with singletons: odds ratio 0.91 (95% CI 0.85–0.96).

Conclusions—Fetal death in one of monozygotic twins has serious implications for survival of the co-twin. Monochorionicity is probably the essential feature of the increased risk to the co-twin. It is imperative that all fetal deaths in multiple

pregnancies are recorded and chorionicity determined if parents are to be adequately counselled.

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Twins are at increased risk of fetal and infant death compared with singleton births.^{1–3} The increased risk is partly the result of the lower birthweight and gestational age at delivery of multiple pregnancies. At particular risk are monozygotic twins who have poorer survival rates than dizygotic twins.^{4–5} Furthermore, if one fetus dies in utero in a twin pregnancy, reports from several case series have shown that the surviving co-twin is at increased risk of death in infancy and major morbidity, such as cerebral palsy, learning disability, and gut atresias.^{6–17} The increased risk for cerebral impairment in the surviving co-twin also has been shown in population based registers of cerebral palsy.^{18–20} In these reports the risk seems to be confined to monozygotic and, in particular, monochorionic twins.

This study aimed to quantify the level of risk for stillbirth and infant death in singleton compared with twin pregnancies, using national data, and to determine the independent effects of zygosity, sex, and birthweight on these risks in twin pregnancies.

Methods

The numbers of all singleton and twin stillbirths, live births, and infant deaths registered for England and Wales, 1982 to 1991 inclusive, were obtained from the Office for National Statistics (ONS). The registration of all births and deaths is a legal requirement, so that ascertainment can be considered to have been virtually complete. These data were for the sex of the child and the birthweight categories <1000 g, 1000–1499 g, 1500–2499 g, ≥2500 g and "birthweight not stated." Data on the twins also included whether they were of same or different sex.

In 1981 a period of industrial action by local registrars of births and deaths resulted in multiplicity of birth not being recorded, so it was decided to begin this study from the time that the data were complete—1982. The analysis was not taken beyond 1991 because the definition of stillbirth changed in October 1992 from 28 to 24 weeks of gestation and stillbirth rates, before and after the change of definition, are not comparable.

All different sex twins are dizygotic. All monozygotic twins are same sex. The Weinberg rule was then applied to the data.²¹ This rule

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Table 1 Like and unlike sex twin pairs by stillbirth/live birth status: England and Wales 1982–91

	Both stillbirths (%)	1 stillbirth 1 live birth (%)	Both live births (%)	Total twin pairs
a Like sex pairs	317 (0.6%)	1294 (2.6%)	47 999 (96.8%)	49 610 (100%)
b Unlike sex pairs	12 (0.1%)	402 (1.9%)	20 748 (98.0%)	21 162 (100%)
a+b Total twin pairs	329 (0.5%)	1696 (2.4%)	68 747 (97.1%)	70 772 (100%)
a-b *Monozygotic pairs	305 (1.1%)	892 (3.1%)	27 251 (95.8%)	28 448 (100%)
2 x b †Dizygotic pairs	24 (0.1%)	804 (1.9%)	41 496 (98.0%)	42 324 (100%)

*Applying the Weinberg rule that, among dizygotic twins, there are an equal number of like sex as unlike sex pairs.

†Based on the assumption that fetal death rates in unlike (dizygotic) sex pairs is the same as in like dizygotic sex pairs.

Table 2 Stillbirth/live birth twin pairs: infant mortality among live births, England and Wales 1982–91

	No of live births	No of neonatal deaths (per 1000 live births)	No of postneonatal deaths (per 1000 live births)	No of infant deaths (per 1000 live births)
a Same sex	1294	81 (62.6)	21 (16.2)	102 (78.8)
b Different sex	402	13 (32.3)	7 (17.4)	20 (49.8)
a+b Total twin pairs	1696	94 (55.4)	28 (16.5)	122 (71.9)
a–b *Monozygotic pairs	892	68 (76.2)	14 (15.7)	82 (91.9)
2b †Dizygotic pairs	804	26 (32.3)	14 (17.4)	40 (49.8)

*Applying the Weinberg rule that, among dizygotic twins, there are an equal number of same sex as different sex pairs.

†Based on the assumption that the number of infant deaths in different (dizygotic) sex pairs is the same as in same dizygotic sex pairs.

states that, among dizygotic twins, there are equal numbers of same sex as there are different sex pairs. Thus:

Total like sex pairs = total monozygotic pairs + like sex dizygotic pairs.

But unlike sex pairs (all of which must be dizygous) = like sex dizygotic pairs. Therefore:

Total like sex pairs = total monozygotic pairs + total unlike sex pairs. Therefore:

Total monozygotic pairs = total like sex pairs – total unlike sex pairs.

Similarly, it was assumed that the risks of fetal and infant death were identical for same sex and different sex dizygotic pairs. Based on this assumption, the number of fetal and infant deaths in monozygotic compared with dizygotic twins can be determined as follows: number of fetal (or infant) deaths in monozygotic twins = number of fetal (or infant) deaths in like sex less the number of fetal (or infant) deaths in unlike sex. Therefore, the number of fetal (or infant) deaths in dizygotic twins is twice the number of fetal (or infant) deaths in different sex twins. The relative risk of fetal and infant death in monozygotic compared with dizygotic twins can be determined, using these numbers.

The Statistical Package for Social Sciences (SPSS) software was used for all the statistical analyses. Relative risks with 95% confidence intervals were estimated. Because birthweight and sex may be confounding variables in any comparison of infant mortality between singletons and mono- and dizygotic twins, a logistic regression analysis with neonatal mortality as the dependent variable and birthweight in the five birthweight categories, sex, and multiplicity (singleton or twin) was carried out. The interaction between sex and multiplicity was also examined. Infants in the “birthweight not stated” category were excluded from the analysis.

Results

For England and Wales, between 1982–91, there were 6 563 834 (6 531 525 live births and 32309 stillbirths) registered singleton deliveries and 70772 registered twin pairs.

Table 1 shows the stillbirth/live birth status of the twins according to whether they were of same or different sex. Based on the Weinberg rule, it can be estimated that 42324 (59.8%) twin pairs were dizygotic and 28448 (40.2%) were monozygotic. The relative risk of both twins being stillborn in monozygotic

compared with dizygotic pairs was 18.91 (95% confidence interval: 12.48 to 28.64; $p < 0.0001$).

The relative risk of a pair comprising one stillbirth and one live birth was also increased in monozygotic compared with dizygotic pairs: 1.63 (95% CI 1.48 to 1.79; $p < 0.0001$).

The overall stillbirth rate in singletons and twins combined over the 10 years 1982–91 was 5.17 per 1000 total births. Of this stillbirth rate, 93.2% can be attributed to singletons, 4.3% to monozygotic twins, and 3.5% to dizygotic twins. (Births in higher order multiple pregnancies were excluded as they would have made only a very marginal difference to the stillbirth rate.)

Among the twin pairs where one was a registered stillbirth and the other live born, the infant mortality rates among the surviving co-twins were higher among mono- than dizygotic pairs (table 2). The relative risk of infant death in monozygotic compared with dizygotic twins was 1.85 (95% CI 1.28 to 2.66; $p < 0.001$). However, the relative risks of the components of infant mortality were: 2.36 (95% CI 1.52 to 3.67; $p < 0.001$) for neonatal mortality and 0.95 (95% CI 0.46 to 1.98; $p = 0.9$, not significant) for postneonatal mortality. It is clear that when one twin is stillborn, all the excess infant mortality among the live borns of mono- compared with dizygotic conceptions occurs in the neonatal period. Because a stillbirth in a twin pair is associated with an adverse effect on neonatal mortality in the live born co-twin, a logistic regression analysis was carried out limited to those twin pregnancies in which both were live born. Neonatal mortality rate as the dependent variable was regressed with birthweight (in five groups), sex, and multiplicity (singleton or twin) as the independent variables. There was a highly significant excess neonatal mortality of boys compared with girls; the odds ratio (OR), after adjusting for birthweight and multiplicity of birth was 1.41 (95% CI 1.37–1.45; $p < 0.0001$). Twins had a highly significant reduction in neonatal mortality compared with singletons after adjusting for birthweight and sex; OR 0.91 (95% CI 0.85–0.96; $p < 0.002$). The sex and multiplicity interaction was not significant; OR 1.06 (95% CI 0.97–1.14). These sex and multiplicity of birth differences in odds ratios may be better appreciated as neonatal mortality rates (table 3) which are based on fitted values from the logistic regression.

Table 3 Birthweight and sex specific neonatal mortality rates per 1000 live births, England and Wales, 1982–91 (fitted values from the logistic regression analysis)

Birthweight group (g)	Girls		Boys	
	Singletons	Twins	Singletons	Twins
<1000	423.0	384.1	595.3	541.9
1000–1499	62.6	56.9	88.3	80.2
1500–1999	16.0	14.5	22.5	20.5
2000–2499	4.3	3.9	6.0	5.5
≥2500	0.7	0.6	1.0	0.9

Discussion

The increased risk of stillbirth and infant mortality among multiple pregnancies and, specifically, among monozygotic multiple pregnancies, is well recognised.^{1–4} The data presented here quantify the level of risk and, because they comprise a decade of national data from registrations that are legally required, ascertainment was complete. The estimates of relative risk and odds ratios will therefore be statistically robust.

When both twins are live born, they were at reduced risk of neonatal mortality for a given birthweight compared with singletons. The likely explanation is that, for a given birthweight, twins are gestationally more mature than singletons. Ideally, comparison of mortality between twins and singletons should adjust for gestational age and not for birthweight but, as gestational age is not recorded at birth registration, the adjustment for gestation could not be made.

The observation that it is monozygotic pregnancies which are at increased risk compared with dizygotic pregnancies, is based on an assumption that the Weinberg rule is valid. It is generally accepted that the rule holds good for large samples, as a result of the blood typing of twins, but there is a significant excess of same sex pairs among dizygotic twins.²² This being so, the excess stillbirth and neonatal death associated with mono- compared with dizygosity will have been under- rather than overestimated. The application of Weinberg's rule to differentiate the number of neonatal deaths in mono- and dizygotic twins may be more contentious, but there does not seem to be any reason why same sex dizygotic twins should be any more or less liable to die in the neonatal period than different sex dizygotic twins.

National birth and death registration data allow only the effect of zygosity, not of chorionicity, to be estimated. However, case reports suggest that among monozygotic twin pregnancies only the monochorionic are at increased risk. Follow up of twins diagnosed by ultrasonography at 10–14 weeks of gestation supports this observation: monochorionic pregnancies have a higher rate of fetal loss before 24 weeks of gestation, perinatal mortality, and premature delivery than dichorionic pregnancies.²³ Among Caucasians, various studies estimate that from 64% to 85% of monozygotic pregnancies are monochorionic.²⁴ If the increased risk is attributable to monochorionicity, the magnitude of the increased relative risks determined from this analysis of national data will have been considerably underestimated. The vastly increased relative risk of both infants being stillborn or of a stillbirth/live birth pair in monozygotic compared with dizygotic pregnancies has important implications for aetiology and for obstetric management. It is unlikely to be attributable to extraneous factors or maternal factors because in such cases both mono- and dizygotic pregnancies should be at equal risk. The increased risk must therefore be inherent in the process that leads to a monozygotic multiple pregnancy.

An hypothesis which would explain the observations is that the division process in a monozygotic multiple pregnancy leads to a chromosomal or other anomalous lethal aberration in one fetus. One mechanism which is partly responsible for the high relative risk of both twins being fetal deaths is feto-fetal transfusion. Another mechanism that has been proposed is thrombo-embolisation in the surviving fetus after the fetal death of its co-twin. A third suggested mechanism is that the moment of fetal death in one twin leads to a profound circulatory response with ischaemic consequences for the co-twin. The ischaemic effects are likely to affect the brain predominantly because of its large size relative to other organs during fetal development, but other organs, notably the gut, kidneys, and the skin, may also be affected. Therefore, as a result of fetal death of one twin, there could be a continuum of damage to the other fetus(es) in monochorionic multiple pregnancies. At one extreme the other fetus may be so compromised that it also dies, thus explaining the high relative risk of both twins dying in utero in monozygotic twin pregnancies. A less serious effect would be that the second fetus is live born, but is so compromised that it succumbs early in infancy, thereby accounting for the increased relative risk of neonatal death in the survivor of a monozygotic pregnancy. The least serious scenario would be that the child survives infancy but has serious long term morbidity. Case reports indicate that the most likely complication is cerebral abnormality presenting as microcephaly, porencephaly, or hydranencephaly and manifest clinically as cerebral palsy and severe learning disability, but congenital intestinal atresias, renal dysplasia, and aplasia cutis have also been described.^{5–16 25–31} The hypothesis can be tested by careful postmortem and histopathological examination of affected fetuses and/or infant deaths. Specifically what needs to be sought in these early deaths is macroscopic and microscopic cerebral abnormality; the intestinal atresias, renal dysplasia, and aplasia cutis are usually self evident.

When one twin dies in utero, the increased risk of fetal death, neonatal mortality, and serious morbidity in the surviving co-twin has important implications for the registration of births. Legally, registration of a fetal death depends on the gestational age of the fetus when it is expelled from the womb (previously 28 weeks but changed to 24 weeks in 1992), not the gestational age at death. However, in practice, this legal requirement is often not met and death of one fetus before 28 (or 24) weeks is not registered if the live co-twin is delivered after the statutory gestational age definition.^{32–35} As a fetus papyraceous may not be recognised or, if recognised, may not be registered, many cases of congenital cerebral, renal, intestinal and cutaneous anomalies will be recorded in apparently singleton pregnancies but will have been caused by early death of a co-twin.

Recent improvements in the resolution of ultrasound examination may allow monochorionic multiple pregnancies to be distinguished

early in gestation. Intrauterine death and/or miscarriage of one fetus in a monochorionic multiple pregnancy may have profound consequences for the surviving fetus(es). As these consequences include neonatal death, severe cerebral, intestinal, renal and cutaneous abnormalities, the information is crucial to the counselling of parents. It may also provide supportive evidence for the hypothesis that a cause of cerebral palsy and several other congenital malformations is fetal death of a monochorionic co-twin³⁶ and may lead to the development of preventive measures.

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