

A Case-control Study of Vanishing Twin as a Risk Factor for Cerebral Palsy

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It has been hypothesized that cerebral palsy of unknown etiology is the result of the death of an unrecognized co-twin — a vanishing twin — in early gestation. We conducted a case-control study of vanishing twin as a risk factor for cerebral palsy of unknown etiology in women who had an obstetric ultrasound during pregnancy. Among mothers of cases, one of 86 had evidence of a vanishing twin on ultrasound, as compared to two of 381 control mothers (odds ratio [OR] 2.2, 95% confidence interval [CI] 0.2–24.8; $p = 0.5$). Bleeding in early pregnancy, which may indicate the loss of a co-twin, was reported by 14 case mothers and 46 control mothers (OR 1.6, 95% CI 0.8–3.0; $p = 0.3$). On the basis of results presented here, the vanishing twin syndrome is unlikely to account for a high proportion of cases of cerebral palsy, but there is insufficient statistical power to draw firm conclusions.

The introduction of obstetric ultrasound scanning has drawn attention to the vanishing twin syndrome in which more than one fetus, or fetal sac, is observed early in gestation, whereas at delivery, there is a singleton birth. Pharoah and Cooke (1997) have hypothesized that the death of a co-twin in early gestation (less than 12 weeks) may put the surviving twin at risk of spastic cerebral palsy and could account for the majority of cases of cerebral palsy of unknown cause. The proportion of pregnancies demonstrating the vanishing twin phenomenon depends on the definition used. Landy and colleagues (1986) identified 7 out of 1000 pregnancies in which 2 sacs were demonstrated on ultrasound prior to 12 weeks gestation, both with fetal heart movements, followed by a single fetus at later gestation. Fetal loss occurred within 2 weeks of the first scan and was usually accompanied by vaginal bleeding. Using a broader definition of vanishing twin, encompassing the presence of an empty sac on ultrasound with no fetal heart pulsation detected, Landy et al. identified 24 out of a 1000 pregnancies demonstrating the phenomenon. In order to test the hypothesis that vanishing twin is a cause of cerebral palsy of unknown etiology, we conducted a case-control study in women who had an obstetric ultrasound scan during pregnancy.

Materials and Methods

Cases comprised all children born in the English counties of Oxfordshire, Berkshire and Northamptonshire between 1990–1993 with a diagnosis of cerebral palsy (ICD-9 classification) that were identified from the population-based Oxford Register of Early Childhood Impairment

(Gaffney et al., 1994). The date of birth and surname of the case were used to locate the delivery register entry of the individual's birth and the information recorded there was used to identify the mothers' obstetric records, including ultrasound reports. Four controls per case were identified from the delivery register matched for date of birth, sex and hospital of birth; these comprised the two individuals of the same sex born just before the case and the two born just after the case. Because information was obtained from obstetric records, rather than relying on self-reporting, problems associated with recall bias are avoided. A broad definition of vanishing twin was used, including the presence of an empty sac (together with a viable fetus) visible on obstetric ultrasound scan.

Information from maternal ultrasound reports and obstetric records was abstracted by research midwives onto structured questionnaires. Data were computerized by a trained clerk using a specially designed entry program. Odds ratios (ORs) were estimated for each variable using unconditional logistic regression and p -values are 2-sided (STATA Corp., 2001). The attributable risk associated with vanishing twin was calculated using standard methods for case-control studies. The confidence intervals for the attributable risk were calculated using methods proposed by Daly (1993). The study was approved by local research ethics committees in all centers.

Results

Of 103 cases of cerebral palsy identified from the Oxford Register of Early Childhood Impairment, 6 were excluded because maternal obstetric records were not found and 6 because there was a known post-natal cause of cerebral palsy. A further 5 were excluded because the mother had not had an ultrasound examination during pregnancy, or the report was not found. Similarly, 8 controls were excluded because obstetric records could not be found and 23 because no ultrasound report was available. The analyses presented here are based on 86 cases without a known cause of cerebral palsy and 381 controls.

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For 13 cases and 66 controls, the gestational age at the time of the ultrasound examination was unknown. Among the remaining 73 cases and 315 controls, the proportion who had their first ultrasound at less than 12 weeks gestation, 12–20 weeks and 21+ weeks, was 12% (9), 75% (55) and 12% (9) respectively for cases and 7% (23), 83% (260) and 10% (32) respectively for controls; the apparent differences were not statistically significant ($p = 0.6$).

One case mother had evidence of a vanishing twin, reported on ultrasound as an irregular sac with no fetal heart at 8 weeks gestation. Among control mothers, 2 women had an ultrasound at 11 and 15 weeks gestation respectively, that reported evidence of an empty sac with no fetal heart (odds ratio [OR] 2.2, 95% confidence interval [CI] 0.2–24.8; $p = 0.5$). The gestational age at delivery of the surviving co-twin was 28 weeks for the case and 40 weeks for both controls. It was not possible to determine if the vanishing twins and surviving infants were monozygotic. If the true relative risk of cerebral palsy associated with vanishing twin is 2.2, and the prevalence in the general population is 24 per 1000 births, as proposed by Landy et al. (1986), then vanishing twins might account for 3% (95% CI 0–36%) of all cases of cerebral palsy of unknown etiology. When analyses were restricted to women known to have had an obstetric ultrasound scan before 12 weeks gestation the vanishing twin phenomenon was demonstrated in 1 of 9 case mothers and 1 of 23 control mothers (OR=2.8, 95% CI 0–117).

Bleeding in early pregnancy, which may indicate the loss of a co-twin, was reported by 14 case mothers and 46 control mothers (OR 1.6, 95% CI 0.8–3.0; $p = 0.3$). Six cases (7%) and 12 controls (3%) were from multiple live births and one additional case was exposed to the death of a co-twin in utero at 27 weeks gestation (OR 2.7, 95% CI 1.0–7.1; $p = 0.03$).

Discussion

The prevalence of vanishing twin recorded in control mothers was 2 in 381 births, or 5.2 per 1000 births. This is lower than the 24 per 1000 identified by Landy et al. (1986), suggesting that we are under-reporting instances of vanishing twin. In 1990–1993, when the cases and controls were born, there was no routine obstetric ultrasound scanning of all pregnant women at any of the study centers. Only a small proportion of women had an ultrasound before 12 weeks gestation and since ultrasound evidence may last less than two weeks, it is possible that we failed to identify the majority of early losses. However, we found no significant excess of reports of early bleeding (which may indicate the loss of a co-twin) among case mothers as compared to control mothers.

To be comparable, the ability to identify a vanishing twin must be the same in both cases and controls and it is likely that this ability depends on the gestational age

at ultrasound scanning. We did not match cases and controls on gestational age at first ultrasound scan, although there was no statistically significant difference between cases and controls in relation to the gestational age at first scan. Restricting the analysis to the small proportion of women who had a scan below 12 weeks did not materially change the odds ratio (2.8), but did diminish the statistical power of the study. Matching cases to controls on the basis of the gestational age at ultrasound scan should be an important consideration in future studies, since this will affect the ability to identify evidence of vanishing twins.

The odds ratio for cerebral palsy associated with vanishing twin identified here (2.2, 95% CI 0.2–24.8), was similar to that found for other types of multiple pregnancy in this study (2.7, 95% CI, 1.0–7.1). These results are compatible with a summary odds ratio (for published studies) of the effect of multiple pregnancy on the risk of cerebral palsy, estimated in a review by Stanley et al. (2000) of 4.5, (95% CI 3.9–5.2). Our results suggest that the vanishing twin syndrome, as defined here, by evidence from obstetric ultrasound scans, might account for a small proportion of cases of cerebral palsy of unknown etiology, but there is insufficient statistical power to draw firm conclusions.

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