Vanishing Twin: A Possible Cause of Cerebral Impairment

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Fetal death in a twin conception during second and third trimester is associated with increased risk of cerebral injury in the surviving twin. The aim of this study is to test the hypothesis that even early fetal losses as a 'vanishing' twin may be associated with an increased risk of cerebral impairment in the surviving twin. The study population comprised 362 pregnant women attending Liverpool Women's Hospital recruited between 1999 and 2001. Women were classified according to the first ultrasound scan into 3 groups: vanishing twin, twin and singleton. The vanishing twin group was further subdivided into 'definite' and 'probable'. Children from these pregnancies were assessed at 1 year of age for their development and neurological function using the Griffiths Mental and Developmental Scales and Optimality score. Children from 229 pregnancies (63.2%) attended the assessment. Information on children from a further 21 (5.8%) pregnancies was obtained through a review of hospital records. Cerebral impairment was found in 2 children from the vanishing twin group, 2 from the twin group and none from the singleton group. When cases with definite vanishing twin are considered there is a significant difference between the vanishing twin and singleton group (relative risk 6.1; 95% confidence interval 1.5–8.3; $p = .03$). An additional study with an increased sample size would enable a more robust conclusion.

Spontaneous fetal loss is a common complication of pregnancy. In multiple pregnancy the fetal loss may be limited to one of the fetuses with survival of the co-conceptus. Fetal death in a twin conception is associated with increased risk of cerebral injury in the surviving twin. Many case series (Anderson et al., 1990; D'Alton et al., 1984; Saito et al., 1999; Yoshida & Soma, 1986), retrospective studies and population-based studies have confirmed this observation (Bajoria et al., 1999; Fusi & Gordon, 1990; Pharoah & Adi, 2000; Rydhström & Ingemarsson, 1993; Santema et al., 1995; Yoshida & Matayoshi, 1990).

Initially it was thought that the increased risk of cerebral impairment manifests only when the fetal death occurred late in pregnancy (Yoshida & Soma, 1986). Subsequent reports noted that even second (Anderson et al., 1990) and first trimester fetal loss (Brodtkorb et al., 2000; Chen et al., 2002; Kapur et al., 1991; Weiss et al., 2004) are associated with adverse consequences for the surviving co-twin.

The increasing use of ultrasonography in the first trimester of pregnancy (Dickey et al., 1990; Landy et al., 1986; Levi, 1976; Robinson & Caines, 1977) has shown that co-fetal loss is much more common in early pregnancy than in second and third trimester. This early fetal loss was termed the 'vanishing twin' (VT). It is hypothesized that even in early fetal loss, the VT may be associated with cerebral impairment in the surviving twin (Pharoah & Cooke, 1997). There have been case reports associating VT with focal cortical sclerosis (Brodtkorb et al., 2000), microcephaly with dysgenesis of corpus callosum and colpocephaly (Chen et al., 2002) and multicystic encephalomalacia (Weiss et al., 2004). However, there are no long-term systematic studies examining the consequences of a VT.

The study reported here tests the hypothesis that VT is associated with increased risk of cerebral impairment in the surviving co-twin.

Materials and Methods

The study cohort comprised women attending the Liverpool Women's Hospital between May 1999 and May 2001. Those found to have a twin conception at their first ultrasound scan were identified. At a subsequent appointment, usually at about 16 weeks' gestation, those with a VT were recruited into the study as the index group. Two additional groups were sought as controls. All women whose twin conceptions continued beyond 20 weeks' gestation were recruited as one control group. A second control group comprised a sample of women with a singleton at the time of first scan. These were matched to

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the nearest week with the index VT cases for gestational age at the time of first scan.

At the end of the recruitment process the ultrasonic images of VT pregnancies were validated by an independent assessor who was blind to the formal report kept in the obstetric case records. Unlike ultrasonographers who had the advantage of visualizing a dynamic image, the independent assessor had access to still images only. Based on these ultrasound scan images, the evidence for VT was classified into 'definite', 'probable', 'possible' and 'negative'. The findings from the independent assessor and the ultrasonographer's report were matched, and where there was agreement the case was classified as definite, and if there was doubt it was classified as probable. Chorionicity was determined whenever possible.

Follow-Up

When the children were approaching 1 year of age, the family's general practitioner (GP) was sent a short questionnaire to determine if the children had experienced problems during the first year of life and whether it was appropriate to contact the mother. This also facilitated tracing the family if there had been a change of address or GP. If the family had changed their GP, the Patient Data Department was approached to obtain the new GP details.

On receiving the GP's response, mothers were sent an information sheet reiterating the details of the project and seeking their cooperation. If there was no response, parents were contacted by telephone and if they agreed to participate, an appointment was made for the assessment of the children. The assessments were conducted in Liverpool Women's Hospital. If the parents were unable to come to the clinic, a home visit was offered. Written consent from the parents was obtained prior to the assessment.

Assessment

The Griffiths' Mental and Developmental scales (Griffiths, 1996) and Optimality score (Haataja et al., 1999) were used for assessment of children attending the clinic. All the assessments were done by a single examiner (DA). If any abnormalities were noted, further confirmation was sought from a neuropediatrician.

Sample Size Calculation

Cerebral palsy (CP) was used as a marker of cerebral impairment and sample size was calculated based on the prevalence of CP in twins and singletons.

Among twin pregnancies the prevalence of monochorionic conceptions is about 20% to 25% (Sebire et al., 2000; Sepulveda et al., 1996) and it was assumed to be the same in VT conceptions. The risk of CP in a monochorionic pregnancy associated with co-twin death is about 25% (Murphy, 1995; Pharoah & Adi, 2000). Therefore the risk of CP from a monochorionic VT pregnancy is 6.3% (60.3 per 1000). In the general population the prevalence of CP in singletons with a birthweight of more than 2500 g is about 1 per 1000 (Surveillance of Cerebral Palsy in Europe, 2000).

Assuming the probability of CP in control singletons to be .001 and in the VT group .06, the sample size was calculated aiming to attain a significance of 5% ($\alpha = .05$) and a power of 80% ($ß = .8$) using four controls per index case. To fulfil these criteria a sample of 58 index cases (VT conceptions) and 232 controls (singletons) was required.

In Liverpool Women's Hospital, approximately 6000 women deliver annually. In a previous pilot study, 22 VT pregnancies were identified in 6 months. Therefore a minimum period of 18 months was required to recruit an adequate number of index cases. To accommodate for probable loss of sample during follow-up, recruitment was maintained for 25 months.

Statistical Analysis

The data obtained from the assessments were entered into an Access database and analysis was done using StatsDirect v 2.4.5. The relative risk (RR) is calculated for categorical data. The Haldane correction was used when any of the cells in the 2×2 tables contained the value 0. The Haldane correction is used to avoid zero error in the calculation of some of the chi-square tests. It involves adding 0.5 to all of the cells of a contingency table if any of the cell expectations would cause a division-by-zero error. Hypothesis testing was done using Fisher's exact test as some of the cells contained values less than 5.

The study was approved by the Liverpool Regional Ethics Committee.

Results

A total of 269 women were found to have a multiple conception at their first ultrasound scan between May 1999 and May 2001. All were approached for recruitment into the study. At a subsequent ultrasound scan there were 85 with a VT (31.6%), 174 twins (64.7%) and 10 triplets (3.7%). Triplets were excluded from further analysis. In the singleton control group 196 women were approached for recruitment into the study. An overview of study population is shown in Figure 1.

The 378 pregnancies that were followed up resulted in 520 live-births. Among the 172 singletons, one was a fetal death after 24 weeks' gestation that was registered as a stillbirth. There were 62 multiple conceptions in which one conceptus vanished. Sixty twin conceptions with a VT resulted in 60 live-births and two triplet conceptions with a VT each delivered two live-births. Two from the VT group died after birth. Among the 144 control twin pairs, both of a monochorionic twin pair were stillborn and in another monochorionic twin pair one fetus died in utero and the other was a live-birth.

Follow-Up at 1 Year of Age

There were 518 children from 374 pregnancies who survived to 1 year of age for follow-up assessment.

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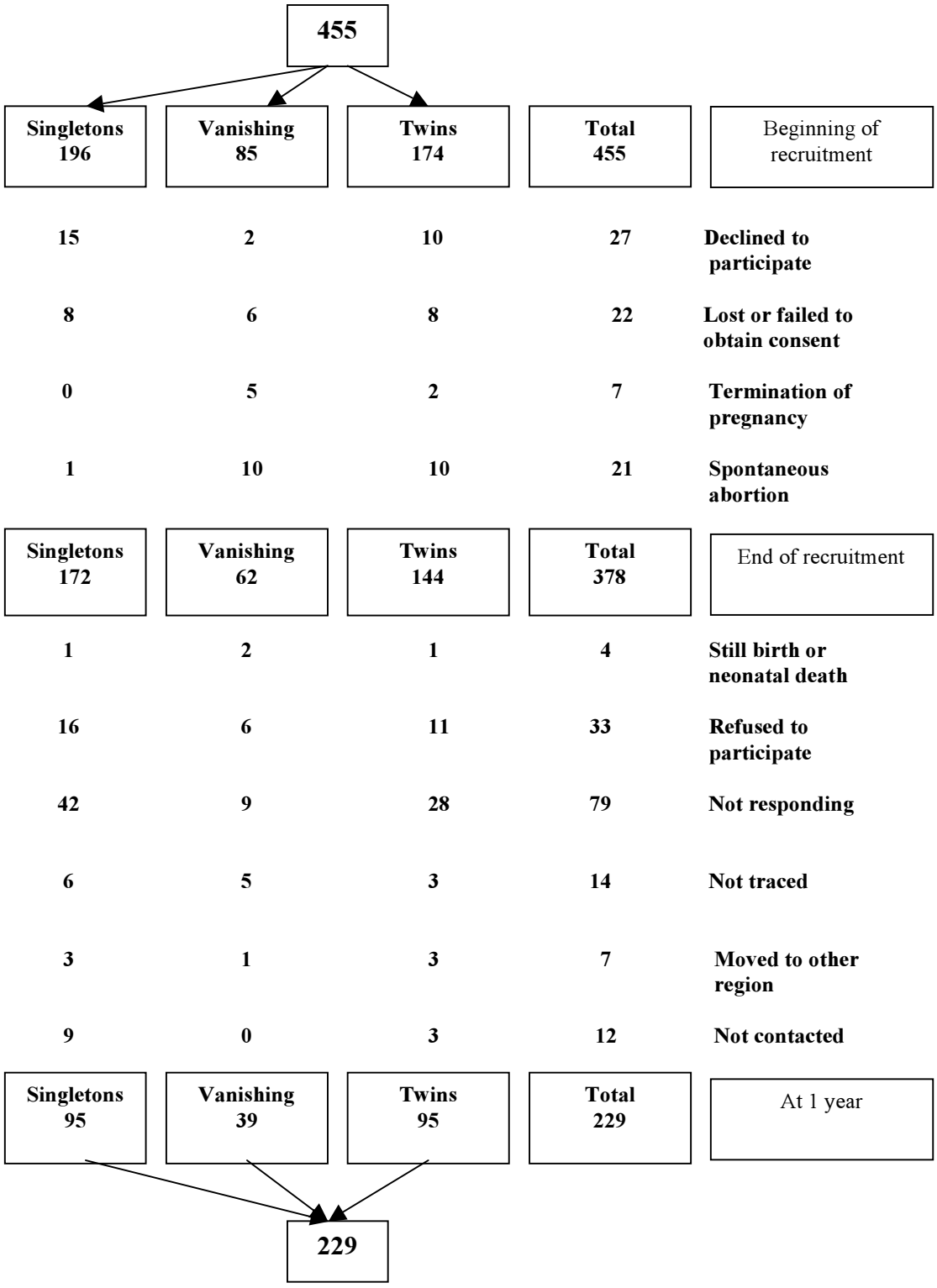

Figure 1
Flow chart of study population.

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Details of eight pregnancies were not passed on owing to failures in the recruitment system. Five were in the singleton control group and three in the twin group (2 dizygotic and 1 monozygotic). On the advice of the GP, four families were not contacted. The reasons mentioned were social concerns or death in the family. All were in the singleton control group. Following these exclusions, 503 children from 362 pregnancies remained for follow-up at 1 year of age.

Response Rate

Of the 362 families, 229 (63.2%) agreed to participate and attended the assessments. The 229 pregnancies that were followed up comprised 95 singletons, 95 twin pairs (73 dizygous, 18 monozygous and 4 zygosity unknown) and 39 VT (10 dizygous, 2 monozygous and 26 zygosity unknown). In one set of twins only one survived and the co-twin died in utero. One triplet conception had a vanishing embryo with two live-births. In total, 324 children were followed up. In 14 children the assessment was incomplete: they were either shy and did not perform the tasks or became too distressed to continue further assessment. One child was not assessed because of incapacity from a fractured arm. The incomplete assessment that was performed on these children did not reveal any developmental delay or disability. A full assessment was performed on 309 children.

Children from the remaining 133 (36.8%) pregnancies were not assessed. In 21 (5.8%), some information was obtained following review of the hospital records, access to which had been granted by the mother at the time of recruitment. In total, reliable information regarding developmental delay or disability was available on children from 250 (69%) pregnancies.

The general characteristics of responders and nonresponders at the time of birth are shown in Table 1. No significant differences in sex, gestational age, birthweight, head circumference, cord pH and neonatal admissions were found.

Vanishing Twin Group

Children from 39 pregnancies underwent formal assessment. In 21 conceptions there was definite early fetal loss and in the remaining 18 it was probable. Children from 38 pregnancies were clinically normal. Their development was age appropriate with no abnormal signs on neurological examination. One child was found to have significant developmental delay which was confirmed by the neuropediatrician.

Although some mothers were unwilling to attend the formal assessment they allowed access to their children's hospital records. Such information was obtained for four children. Three were normal (probable VT) and one child (definite VT) was noted to have severe developmental delay and seizures.

Twins

One hundred and eighty-two children from 95 twin pregnancies underwent formal assessment. No abnormalities were noted in 181 children. One child had developmental delay. Hospital records were reviewed for nine twin pairs who were not formally assessed. One child was noted to have developmental problems.

Singletons

The 95 singleton children who underwent formal assessment were all found to have normal development and neurological function.

The hospital notes of eight children not formally assessed were reviewed. One child was noted to have developmental delay secondary to cerebral damage due to postnatal hypoxic injury while receiving intensive care.

Chorionicity

In multiple pregnancies, chorionicity is an important determinant of outcome. Among the twin pregnancies, chorionicity was recorded in 140 (97.2%) of the 144. Of the 140 twin pregnancies, 112 (80%) were dichorionic and 28 (20%) monochorionic. Among the 62 VT pregnancies, chorionicity was recorded at scan in 24 (38.7%). Twenty (83.3%) were dichorionic and four (16.7%) monochorionic.

Table 1

Comparison of General Characteristics of Responders and Nonresponders

	Responders	Nonresponders
Number		
Singletons	95	76
VT	40	22
Twins	189	96
Sex (M/F)		
Singletons	52/43	34/42
VT	24/16	11/11
Twins	105/84	56/40
Gestational age (weeks)		
Singletons	39.4	39.2
VT	39.5	38.5
Twins	35.3	34.7
Birthweight (grams)		
Singletons	3479	3448
VT	3430	3321
Twins	2411	2368
Head circumference (cm)		
Singletons	34.8	35.0
VT	34.4	34.3
Twins	32.4	31.9
Cord pH		
Singletons	7.34	7.34
VT	7.30	7.34
Twins	7.32	7.29
Neonatal admissions		
Singletons	1 (1%)	0 (0%)
VT	1 (2.5%)	0 (0%)
Twins	60 (31.7%)	32 (33.3%)

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Hypothesis Testing

When only cases where VT was diagnosed with certainty were taken into account, there was a significant difference between VT and singleton groups. When cases where diagnosis of VT was probable were included, however, there was no significant difference between the VT group and control singleton or twin groups (Table 2).

Discussion

The current study tested the hypothesis that the early loss of a fetus in a twin conception incurs an increased risk of cerebral impairment in the surviving twin. Although the VT phenomenon has long been recognized, there are few that reported on the long-term effects on the surviving co-twin.

The observations from this study do not provide unequivocal support of the hypothesis. The rationale of the hypothesis is that some twin conceptions are monochorionic and have placental vascular anastomoses. These allow intertwin vascular exchange, the feto-fetal transfusion syndrome. In second and third trimesters such anastomoses were noted to result in hemodynamic instability leading to fetal death or ischemic cerebral damage in either or both twins. Twin reversed arterial perfusion (TRAP) has been demonstrated as early as 12 weeks suggesting that these anastomoses are functional from very early in gestation (Kamitomo et al., 2004; Schwarzler et al., 1999). However, the precise timing of when the anastomoses become functional is unclear. It is plausible that cerebral impairment in the surviving co-twin that has been noted in later gestation may also occur in early gestation as a result of feto-fetal hemodynamic instability.

At 1 year of age, two children in the VT group, one in the singleton group and two in the twin group had neurodevelopmental problems. The neurological abnormality noted in the child in the control singleton group was of postnatal origin. When only definite VT cases were considered there was significant association with cerebral impairment compared to control singleton. However, these findings do not provide firm evidence to support the hypothesis. This may be attributable to incomplete case ascertainment, inadequate sample size or loss to follow-up.

The diagnosis of VT is fraught with difficulties. Loss of one fetus in a twin conception may occur as early as 6 weeks and may be asymptomatic. It has been reported that, in 80% of cases, the event occurs before 8 weeks of gestation and the remaining between the 9th and 11th week (Rodríguez-González et al., 2002). In spontaneous pregnancies scanning is rarely done so early in gestation. In the present study, initial ultrasound scans are done at about 12 weeks' gestation. In the interim 6- to 12-week gestation period, the gestational sac is likely to undergo changes leading to loss of vital signs needed to diagnose and differentiate true gestational sacs from artefacts. Similar difficulties have been reported in previous studies which are likely to account for variations in the prevalence rates of VT (Dickey et al., 1992). Consequent to the difficulties in the diagnosis of the VT, in only 36 of the 62 conceptions could the diagnosis be made with certainty. Therefore the data were analyzed including and excluding the probable cases. When only cases with definite VT were taken into account, there was a significant difference in cerebral impairment between the VT group (2/22) and the singleton group (0/103). This observation could be taken as confirming the hypothesis. However, a Type I statistical error, that is, falsely observing a significant difference, is also possible. The prevalence of VT pregnancy among the multiple conceptions was 31.5%. Given this high prevalence, a Type I error should be considered. When the data were analyzed using both definite and probable cases the difference between VT and singleton groups was no longer significant.

Monochorionicity is an important factor underpinning the patho-physiological mechanisms of the proposed hypothesis. However, the recording of chorionicity among VT conceptions was incomplete. Many of those recorded were dichorionic and the frequency of monochorionic conceptions was lower than expected. A possible explanation is that in a

Table 2

Comparison of Disability in Vanishing Twins and Controls Groups of Twins and Singletons

Index group (Disabled/total number)	Comparison group (Disabled/total number)	Relative risk (confidence intervals)	Fisher's Exact Test *p* value
Definite VT	Singletons	6.1 (1.5–8.3)	.03*
(2/22) (9%)	(0/103) (0%)		
Definite and probable VT	Singletons	3.5 (0.9–4.1)	.08 *ns*
(2/43) (4.6%)	(0/103) (0%)		
Definite VT	Twins	3.1 (0.9–6.3)	.14 *ns*
(2/22) (9%)	(2/104) (1.9%)		
Definite and probable VT	Twins	1.7 (0.5–3.3)	.4 *ns*
(2/43) (4.6%)	(2/104) (1.9%)		

Note: *significant; *ns* = not significant.

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monochorionic twin conception, fetal loss of both twins may have been more common than in dichorionic gestations. A report in which 43 of the 178 twin pregnancies identified before 12 weeks' gestation were associated with the intrauterine death of one fetus supports this contention. Nine were monochorionic pregnancies with only one reaching term gestation and the remainder were complicated by loss of the other fetus within 1 to 3 weeks (Malinowski et al., 2005).

In addition to the problems of case ascertainment, the power of the study was also affected by the failure to recruit an adequate number of controls within the study period. The recruitment of controls fell short because of failure to match the gestational age of index cases at the time of the initial ultrasound scan. Only 74% of the controls required were recruited. The final recruitment of 62 VT cases and 172 singleton controls (2.7 controls per index case) adversely affected the power of the study.

The power of the study was further affected by a poor response rate of 63.2%. Of those who refused to participate by allowing examination of the child, 21 (5.8%) gave permission to access the hospital records which allowed validation and provided additional information to that given by the GP.

The attenuation of the sample in follow-up studies is not uncommon. Losses up to 30% or more have been reported (Ericson & Kallen, 1998; O'Callaghan et al., 1996). Several reasons could account for the loss at follow-up. Infants who required medical attention at birth are likely to return for follow-up because parents wish to ensure optimal health. Most children were normal and attendance merely to fulfil a research objective may have been felt unnecessary. Multiple births, compared with singletons, present additional problems of time constraints, difficulties in obtaining transportation and care of the siblings while the parents are attending the assessment. The assessment of each child took about an hour and was particularly burdensome when more than one child had to be assessed. To mitigate these difficulties, appointments were offered for a day and time most convenient to the parents. Transportation and nursery care for siblings were arranged where necessary. Those who found it difficult to visit the hospital were offered a home visit. Despite these endeavours the response rate was poor.

Although it is difficult to be certain, the nonresponders are unlikely to affect the results. The gestational age, birthweight and neonatal outcome of the nonresponders does not differ significantly from those who attended the assessment. The partial information that is available (through GP responses to the questionnaire) on 79 of the 133 who did not respond suggests that, except for two from the twin group, the remainder were normal.

The findings from this study are similar to that of a retrospective case control study where evidence of CP was used as a marker of cerebral impairment. One case of CP was noted among 86 mothers with VT on ultrasound scan as compared to two of 381 control mothers suggesting that there was no association between VT and CP (Newton et al., 2003). This study also suffered from inadequate power. Another large study, involving 642 VT, 5237 singletons and 3678 twins born following assisted reproductive technique (ART), found no excess risk of neurological sequelae in survivors of VT compared to singletons (Pinborg et al., 2005). However, such a result could be expected as the majority of multiple conceptions from ART are dizygotic.

This study does not provide sufficient evidence to suggest that VT is associated with cerebral impairment in the surviving twin. Although, when cases with definite VT are considered, a statistically significant association was noted. The lack of statistical power does not allow a more robust conclusion to be made. Further studies, using a larger sample and better ascertainment of VT and chorionicity by earlier ultrasound scanning preferably at a gestational age of 6 weeks, would remedy this deficiency. Increasing the sample size, performing an early booking scan, improving the follow-up rate and extending the length of follow-up are some of the measures that will be needed to confirm or refute the hypothesis. Routine reporting and recording of the vanishing twin would enable further testing of the hypothesis.

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References

Anderson, R. L., Golbus, M. S., Curry, C. J., Callen, P. W., & Hastrup, W. H. (1990). Central nervous system damage and other anomalies in surviving fetus following second trimester antenatal death of co-twin. *Prenatal Diagnosis, 10*, 513–518.

Bajoria, R., Wee, L. Y., Anwar, S., & Ward, S. (1999). Outcome of twin pregnancies complicated by single intrauterine death in relation to vascular anatomy of monochorionic placenta. *Human Reproduction, 14*, 2124–2130.

Brodtkorb, E., Myhr, G., & Gimse, R. (2000). Is monochorionic twinning a risk factor for focal cortical dysgenesis? *Acta Neurologica Scandinavica, 102*, 53–59.

Chen, C. P., Lin, S. P., & Chiu, N. C. (2002). Microcephaly with dysgenesis of corpus callosum and colpocephaly in the survivor after the first-trimester death of a monochorionic co-twin. *Prenatal Diagnosis*, *22*, 634–635.

https://doi.org/10.1375/twin.10.1.202 Published online by Cambridge University Press

D'Alton, M. E., Newton, E. R., & Cetrulo, C. L. (1984). Intrauterine fetal demise in multiple gestation. *Acta Geneticae Medicae et Gemellologiae, 33,* 43–49.

Dickey, R. P., Olar, T. T., Curole, D. N., Taylor, S. N., Rye, P. H., & Matulich, E. M. (1990). The probability of multiple births when multiple gestational sacs or viable embryos are diagnosed at first trimester ultrasound. *Human Reproduction, 5*, 880–882.

Dickey, R. P., Olar, T. T., Taylor, S. N., Curole, D. N., Rye, P. H., Matulich, E. M., & Dickey, M. H. (1992). Incidence and significance of unequal gestational sac diameter or embryo crown-rump length twin pregnancy. *Human Reproduction*, *7*, 1170–1172.

Ericson, A., & Kallen, B. (1998). Very low birthweight boys at the age of 19. *Archives of Disease in Childhood Fetal Neonatal Edition*, *78,* F171–174.

Fusi, L., & Gordon, H. (1990). Twin pregnancy complicated by single intrauterine death. Problems and outcome with conservative management. *British Journal of Obstetrics and Gynaecology, 97,* 511–516.

Griffiths, R. (1996). *The Griffiths Mental Developmental Scales: From birth to 2 years*. Oxon: The Test Agency.

Haataja, L., Mercuri, E., Regev, R., Cowan, F., Rutherford, M., Dubowitz, V., & Dubowitz, L. (1999). Optimality score for the neurologic examination of the infant at 12 and 18 months of age. *Journal of Pediatrics, 135,* 153–161.

Kamitomo, M., Kouno, S., Ibuka, K., Oku, S., Sueyoshi, K., Maeda, T., & Hatae, M. (2004). First-trimester findings associated with twin reversed arterial perfusion sequence. *Fetal Diagnosis and Therapy, 19*, 187–190.

Kapur, R. P., Mahony, B. S., Nyberg, D. A., Resta, R. G., & Shepard, T. H. (1991). Sirenomelia associated with a 'vanishing twin'. *Teratology, 43,* 103–108.

Landy, H. J., Weiner, S., Corson, S. L., Batzer, F. R., & Bolognese, R. J. (1986). The 'vanishing twin': Ultrasonographic assessment of fetal disappearance in the first trimester. *American Journal of Obstetrics and Gynecology, 155,* 14–19.

Levi, S. (1976). Ultrasonic assessment of the high rate of human multiple pregnancy in the first trimester. *Journal of Clinical Ultrasound, 4,* 3–5.

Malinowski, W., Koktysz, R., & Stawerski, P. (2005). Intrauterine death of one fetus during the first trimester of monochorionic diamniotic twin gestation. *Ginekologia Polska, 76*, 54–60.

Murphy, K. W. (1995). Intrauterine death in a twin: Implications for the survivor. In R. H. Ward & M. Whittle (Eds.), *Multiple pregnancy* (pp. 218–230). London: RCOG Press.

Newton, R., Casabonne, D., Johnson, A., & Pharoah, P. (2003). A case-control study of vanishing twin as a risk factor for cerebral palsy. *Twin Research, 6,* 83–84.

O'Callaghan, M. J., Burns, Y. R., Gray, P. H., Harvey, J. M., Mohay, H., Rogers, Y. M., & Tudehope, D. I. (1996). School performance of ELBW children: A controlled study. *Developmental Medicine and Child Neurology, 38*, 917–926.

Pharoah, P. O. D., & Adi, Y. (2000). Consequences of in-utero death in a twin pregnancy. *Lancet, 355,* 1597–1602.

Pharoah, P. O. D., & Cooke, R. W. I. (1997). A hypothesis for the aetiology of spastic cerebral palsy - The vanishing twin. *Developmental Medicine and Child Neurology, 39,* 292–296.

Pinborg, A., Lidegaard, O., la Cour Freiesleben, N., & Andersen, A. N. (2005). Consequences of vanishing twins in IVF/ICSI pregnancies. *Human Reproduction, 20,* 2821–2829.

Robinson, H. P., & Caines, J. S. (1977). Sonar evidence of early pregnancy failure in patients with twin conceptions. *British Journal Obstetrics and Gynaecology, 84,* 22–25.

Rodríguez-González, M., Serra, V., Garcia-Velasco, J. A., Pellicer, A., & Remohi, J. (2002). The 'vanishing embryo' phenomenon in an oocyte donation programme. *Human Reproduction, 17*, 798–802.

Rydhström, H., & Ingemarsson. (1993). Prognosis and long-term follow-up of a twin after antenatal death of the co-twin. *Journal of Reproductive Medicine, 38,* 142–146.

Saito, K., Ohtsu, Y., Amano, K., & Nishijima, M. (1999). Perinatal outcome and management of single fetal death in twin pregnancy: A case series and review. *Journal of Perinatal Medicine, 27,* 473–477.

Santema, J. G., Swaak, A. M., & Wallenburg, H. C. S. (1995). Expectant management of twin pregnancy with single fetal death. *British Journal of Obstetrics and Gynaecology, 102,* 26–30.

Schwarzler, P., Ville, Y., Moscosco, G., Tennstedt, C., Bollmann, R., & Chaoui, R. (1999). Diagnosis of twin reversed arterial perfusion sequence in the first trimester by transvaginal color Doppler ultrasound. *Ultrasound in Obstetrics and Gynecology, 13*, 143–146.

Sebire, N. J., Souka, A., Skentou, H., Geerts, L., & Nicolaides, K. H. (2000). First trimester diagnosis of monoamniotic twin pregnancies. *Ultrasound in Obstetrics and Gynecology, 16,* 223–225.

Sepulveda, W., Sebire, N. J., Hughes, K., Odibo, A., & Nicolaides, K. H. (1996). The lambda sign at 10–14 weeks of gestation as a predictor of chorionicity in twin pregnancies. *Ultrasound in Obstetrics and Gynecology, 7,* 421–423.

StatsDirect Ltd. (2002). StatsDirect statistical software. England: Author. Retrieved from http://www.statsdirect.com

Surveillance of Cerebral Palsy in Europe (SCPE). (2000). Surveillance of cerebral palsy in Europe: A collaboration of cerebral palsy surveys and registers.

Developmental Medicine and Child Neurology, 42, 816–824.

Weiss, J. L., Cleary-Goldman, J., Tanji, K., Budorick, N., & D'alton, M. E. (2004). Multicystic encephalomalacia after first-trimester intrauterine fetal death in monochorionic twins. *American Journal of Obstetrics and Gynecology, 190,* 563–565.

Yoshida, K., & Matayoshi, K. (1990). A study on prognosis of surviving cotwin. *Acta Geneticae Medicae et Gemellologiae, 39,* 383–387.

Yoshida, K., & Soma, H. (1986). Outcome of the surviving cotwin of a fetus papyraceus or of a dead fetus. *Acta Geneticae Medicae et Gemellologiae, 35,* 91–98.

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