dispersion, but would we really expect that death, even cardiovascular death, would be predicted by the phenomenon in patients with peripheral vascular disease? I did not. I imagined that peripheral vascular disease was associated with occult (or overt) coronary artery disease and that death might arise by various mechanisms: infarction, failure, or arrhythmias. If QT dispersion predicted only the latter I would have expected that any mortality related to QT dispersion would be lost in other fatal end points. My concept seems wrong, or at least it is not supported by the present study. I lay considerable store by biological plausibility, and I look to corroborating data and to more detailed analysis of how patients die before I would be fully comfortable with the results.

If QT dispersion is really so specific and so sensitive, however, it may mean that ventricular fibrillation is more prevalent than we currently acknowledge. QT dispersion may reflect a threshold measure of vulner-

ability to ventricular fibrillation. Thus in a patient with peripheral vascular disease in whom the myocardium is affected in such a way as to disturb repolarisation a propensity to ventricular fibrillation is established and may be revealed by a variety of triggers, including ischaemia.

Our prognostic assessment of patients is improving, but we have little or nothing to offer as protection. Perhaps new information contained in QT dispersion analysis will open new therapeutic directions. We read and write such comments all too often with little realistic prospect that things will change. This time, however, I am optimistic. QT dispersion has been unnoticed for decades. It is proving important and is our only non-invasive marker of regional variations of refractoriness. It may be that regardless of aetiology it can reflect a propensity to ventricular fibrillation. In this simple tool we may be glimpsing the electrophysiological Holy Grail.

Twin births to mothers who are twins: a registry based study

Paul Lichtenstein, Petra Otterblad Olausson, A J Bengt Källén

Abstract

Objectives—To estimate the risk of having twin infants for mothers who are twins; to investigate the genetic influence on twinning.

Design—Retrospective study of multiple births in two nationwide registries.

Setting—Sweden.

Subjects—Multiple births among 31 586 deliveries between 1973 and 1991 to women who were twins.

Main outcome measures—Numbers of monozygotic and dizygotic twin births expected and estimated.

Results—Women who are dizygotic twins have a moderately increased risk of having twins (relative risk 1.30, 95% confidence interval 1.14 to 1.49) which seems to be completely the result of dizygotic twinning. When a mother is a monozygotic twin, her risk of having twins of the same sex is significantly increased (1.47; 1.10 to 1.97). This is the result of an excess of monozygotic twins (39 pairs estimated, 18 expected).

Conclusion—Women who are twins have an increased risk of giving birth to twins. Genetic components of monozygotic and dizygotic twinning seem to be independent.

Introduction

It is generally agreed that genetic factors are important for dizygotic but not for monozygotic twinning. This has not yet been thoroughly investigated.

Among women who have already given birth to twins the risk for further twin births is increased even after age effects are controlled for.^{1,4} The risk seems to exist only for dizygotic twinning.^{1,4,5} A genetic influence is indicated by the increased number of twin births among female relatives of women who had given birth to dizygotic twins.^{1,4,6,7} A study of genealogical records in Salt Lake City, USA, found a twinning rate of 1.45% among mothers who had a twin brother (dizygotic twins) and 1.65% for their sisters, compared with the rate of 0.69% for fathers who had a twin sister.⁷

No firm evidence exists for a genetic influence on monozygotic twinning, although interview studies of

mothers of monozygotic twins report an excess of monozygotic twins among the mothers' relatives.^{4,6} Increased monozygotic twinning rates have also been reported in selected pedigrees.^{8,9}

Most evidence is based on either archival studies or self reports from twins or parents of twins. Both methods may give biased results. Archival studies may underreport twin maternities because stillbirths or early perinatal deaths of one twin in a pair (which occur more often in twin than in singleton deliveries) may be recorded as singleton births.⁴ Interview studies may overestimate twinning rates among first degree relatives in twin families, most likely owing to a heightened awareness of twinning, even if one of the twins was stillborn or died early. This may explain the relatively odd finding of a paternal role in dizygotic twinning as well as the purported common aetiology of monozygotic and dizygotic twinning.⁴

Methods

This study is based on a linkage of two nationwide Swedish registries: the Swedish twin registry,¹⁰ which encompasses data on all twins born in Sweden during the years 1926 to 1991, and the medical birth registry,¹¹ covering 99% of all births in Sweden since 1973. Record linkage identified the female twins born 1926 to 1972 who gave birth in Sweden between 1973 and 1991.

The twin registry contains information on the sex of the twins and, for people born before 1959, zygosity determined on the basis of childhood resemblance.¹² Zygosity was verified with serological data for 99% of the monozygotic and 92% of the dizygotic twins in a subsample.¹³ A high level of validity of this technique has been reported by others.^{14,15}

The year of birth, maternal age, parity, and the number of infants in the birth were obtained from the medical birth registry. The observed numbers of multiple births was compared with expected numbers, which were calculated from the rate of multiple births in the medical birth registry stratified by maternal age and parity.

The estimated rate of monozygosity was based on Weinberg's assumption of equal numbers of same sex and different sex dizygotic twins.² Thus, the number of

Karolinska Institute,
Institute for Environmental
Medicine, Box 210, 171 77
Stockholm, Sweden
Paul Lichtenstein, research
associate

Centre for Epidemiology,
National Board of Health
and Welfare, 106 30
Stockholm, Sweden
Petra Otterblad Olausson,
senior administrative officer

Tornblad Institute,
University of Lund,
Biskopsg 7, 223 62 Lund,
Sweden
A J Bengt Källén, professor
emeritus

Correspondence to:
Dr Lichtenstein.

BMJ 1996;312:879-81

monozygotic twins was estimated as the total number of twins minus twice the number of different sex twins. Although Weinberg's assumption has been questioned,¹⁶ the potential bias for this study is negligible because there is no reason to assume different biases among mothers who are twins and mothers who are singletons.

Results

The odds ratio for having a same sex and different sex twin delivery for each maternal age or parity group is shown in figure 1. The maternal age effect on dizygotic twinning (clearer among the different sex twins because of inclusion of monozygotic deliveries among same sex twins), the decline in odds ratio among women above 40, and the parity effect have been described by Bulmer.¹

In table 1, the births have been divided into groups by maternal twin type. Overall, the twinning rate is 28% greater than in the general population.

Dizygotic mothers have a significantly increased risk of twinning. The risk increase is stronger for different sex twins than same sex twins. The estimated number of monozygotic twin births was not higher than the number expected, but the estimated number of dizygotic twin births was greater than the expected

Fig 1—Odds ratio in each maternal age group versus all other age groups (stratified by year of birth and parity) and in each parity group versus all other parity groups (stratified by maternal age) for having a twin delivery for all women in the medical birth registry, Sweden. Odds ratios are presented separately by type of delivery; 95% confidence intervals are marked with vertical bars

Key messages

- It is generally agreed that genetic factors are important for dizygotic but not for monozygotic twinning
- Women who themselves are dizygotic twins have an increased risk of giving birth to dizygotic twins
- Women who themselves are monozygotic twins have an increased risk of having monozygotic twins
- The genetic components in monozygotic and dizygotic twinning are independent

number (table 1). The ratio of estimated to expected number of dizygotic twins (1.63) was the same as for different sex twins.

For monozygotic mothers the number of same sex twin births was significantly increased (relative risk 1.47, 95% confidence interval 1.10 to 1.97). This is probably due to monozygotic twinning, as the ratio of estimated to expected number of monozygotic twins was 2.17 (39/18.0). With five births of different sex twins to monozygotic mothers there is a 95% probability that the total number of births of dizygotic twins will not exceed 18. The minimum number of monozygotic pairs is then 31—the total number of twin deliveries (49) minus the maximum number of dizygotic deliveries (18)—which clearly is in excess of the expected number, 18.0.

Discussion

The risk of mothers who are dizygotic twins giving birth to dizygotic twins is significantly increased even after age and parity have been controlled for. These results are compatible with previously reported increased twinning in dizygotic twins and their relatives.^{1,2,4,6,7} The underlying mechanism for dizygotic twinning is multiple ovulation,¹⁷ which has been shown to be affected by genetic factors.¹⁸ Segregation analyses have indicated that an X linked gene in sheep¹⁹ and an autosomal gene in humans²⁰ affect

Table 1—Number and type of births to Swedish mothers who were twins. Expected numbers were calculated after stratification by maternal age and parity

Offspring	Mother's zygosity			
	Dizygotic	Monozygotic	Unknown	Total
Singletons	17 830	4360	9033	31 223
Twins:				
No observed	212	49	98*	359
No expected	163.0	41.8	74.7	279.5
Risk ratio (95% CI)	1.30 (1.14 to 1.49)	1.17 (0.89 to 1.55)	1.31 (1.08 to 1.60)	1.28 (1.16 to 1.42)
Same sex:				
No observed	138	44	64	246
No expected	117.6	29.9	54.5	202.0
Risk ratio (95% CI)	1.17 (0.99 to 1.39)	1.47 (1.10 to 1.97)	1.17 (0.92 to 1.50)	1.22 (1.07 to 1.37)
Different sex:				
No observed	74	5	33	112
No expected	45.3	11.9	20.1	77.3
Risk ratio (95% CI)	1.63 (1.30 to 2.05)	0.42 (0.14 to 0.98)	1.64 (1.17 to 2.30)	1.45 (1.21 to 1.74)
Monozygotic:				
No estimated	64	39	31	134
No expected	72.3	18.0	34.4	124.7
Dizygotic:				
No estimated	148	10	66	225
No expected	90.6	23.8	40.2	154.6
Triplets	2	1	0	3
Quadruplets	0	0	1	1

CI=Confidence interval.

*In one twin pair, the sex of one twin was unknown.

multiple birth. Familial occurrences of dizygotic twinning found in this and other epidemiological studies are at least in part due to genetic factors.

The risk of twin births to monozygotic mothers was not significantly increased, but monozygotic mothers had significantly more same sex twin births. Comparison of estimated and expected numbers of monozygotic twin births suggests that this increase is a result of monozygotic twinning. Although other studies have suggested a familial component in monozygotic twinning, samples have been small and the methods susceptible to recall bias.^{4,6}

This population based study shows that women who are twins have an increased risk of giving birth to twins. Contrary to results based on self reports,⁴ this registry based study, free from recall bias, does not support the existence of a common aetiology for monozygotic and dizygotic twinning.

Funding: The Swedish twin registry is supported by grants from the John D and Catherine T MacArthur Foundation and the Swedish Council for Planning and Coordination of Research (FRN).

Conflict of interest: None.

- 1 Bulmer MG. *The biology of twinning in man*. Oxford: Clarendon Press, 1970.
- 2 Weinberg W. Beiträge zur Physiologie und Pathologie der Mehrlingsgeburten bei Menschen. *Pfluegers Arch ges Physiol* 1901;88:346-430.
- 3 Weinberg W. Die Anlage zur Mehrlingsgeburt beim Menschen und ihre Vererbung. *Arch Rass u ges Biol* 1909;6:322-39, 470-82, 609-30.
- 4 Parisi P, Gatti M, Prinzi G, Caperna G. Familial incidence of twinning. *Nature* 1983;304:626-8.
- 5 Nylander PPS. The inheritance of DZ twinning: a study of 18 737 maternities in Ibadan, Western Nigeria. *Acta Genet Med Gemellol* 1970;19:36-9.

- 6 Parazzini F, Tozzi L, Ferraroni M, Bocciolone L, Molteni E, Moreschi C, et al. Risk factors for multiple births. *Acta Obstet Gynecol Scand* 1993;72:177-80.
- 7 Wyshak G, White C. Genealogical study of human twinning. *Am J Public Health* 1965;55:1586-93.
- 8 Carmelli D, Hasstedt S, Andersen S. Demography and genetics of human twinning in the Utah Mormon genealogy. In: Gedda L, Parisi P, Nance WE, eds. *Twin research 3: twin biology and multiple pregnancy*. New York: Alan Liss, 1978: 81-93.
- 9 Philippe P. Genetic epidemiology of twinning: a population-based study. *Am J Med Genet* 1985;20:97-105.
- 10 Cederlöf R, Lörich U. The Swedish Twin Registry. In: Gedda L, Parisi P, Nance WE, eds. *Twin research 3: twin biology and multiple pregnancy*. New York: Alan Liss, 1978: 189-95.
- 11 Cnattingius S, Ericson A, Gunnarskog J, Källén B. A quality study of a medical birth registry. *Scand J Soc Med* 1990;18:143-8.
- 12 Medlund P, Cederlöf R, Floderus-Myrthed B, Friberg L, Sörensen S. A new Swedish twin registry. *Acta Med Scand* 1976;600(suppl):1-111.
- 13 Cederlöf R, Friberg L, Jonsson E, Kaij L. Studies on similarity diagnosis in twins with the aid of mailed questionnaires. *Acta Genet Med Gemellol* 1961;11:338-62.
- 14 Crumpacker DW, Cederlöf R, Friberg L, Kimberling WJ, Sörensen S, Vandenberg SG, et al. A twin methodology for the study of genetic and environmental control of variation in human smoking behavior. *Acta Genet Med Gemellol* 1979;28:173-95.
- 15 Sarna S, Kaprio J, Sistonen P, Koskenvuo M. Diagnosis of twin zygosity by mailed questionnaire. *Hum Hered* 1978;28:241-54.
- 16 James WH. The current status of Weinberg's differential rule. *Acta Genet Med Gemellol* 1992;41:33-42.
- 17 Millham S. Pituitary gonadotrophin and dizygotic twinning. *Lancet* 1964;ii:566.
- 18 Montgomery GW, Crawford AM, Pentz JM, Dodds KG, Ede AJ, Henry HM, et al. The ovine Booroola fecundity gene (Fecb) is linked to markers from a region of human chromosome 4q. *Nature Genet* 1993;4:410-4.
- 19 Davis GH, McEwan JC, Fennessy PF, Dodds KG, Farquhar PA. Evidence for the presence of a major gene influencing ovulation rate on the X chromosome of sheep. *Biol Reprod* 1991;44:620-4.
- 20 Derom R, Orlebeke J, Eriksson A, Thiery M. The epidemiology of multiple births in Europe. In: Keith LG, Papiernik E, Keith DM, Luke B, eds. *Multiple pregnancy: epidemiology, gestation and perinatal outcome*. New York: Parthenon, 1995:145-62.

(Accepted 24 January 1996)

Haem iron intake in 12-36 month old children depleted in iron: case-control study

Michael Mira, Garth Alperstein, Margaret Karr, Geetha Ranmuthugala, Jane Causer, Anna Niec, Anne-Marie Lilburne

Division of General Practice, Central Sydney Area Health Service, Balmain New South Wales 2041 Australia
Michael Mira, director
Margaret Karr, research officer
Jane Causer, research medical officer

Community Health Services, Central Sydney Area Health Service, Royal Prince Alfred Hospital, Camperdown, New South Wales 2050 Australia
Garth Alperstein, area paediatrician
Anna Niec, dietitian
Anne-Marie Lilburne, dietitian

National Centre for Epidemiology and Population Health, Australian National University, Canberra Australia
Geetha Ranmuthugala, research student

Correspondence to: Professor Mira.

BMJ 1996;312:881-3

Abstract

Objective—To compare the intakes of haem and non-haem iron in iron depleted and iron replete children.

Design—Case-control study.

Setting—Early Childhood Centres and a long day care centre in Sydney, Australia.

Subjects—Children aged 12-36 months depleted in iron and controls matched for age and sex.

Mean outcome measures—Iron status by using plasma ferritin concentration. A three day weighed dietary intake record completed by the parents. Risk factors for iron deficiency assessed by questionnaire.

Results—Fifty six iron depleted and 68 iron replete children participated. The average daily intake of haem iron was significantly lower in the iron depleted group ($t=2.392$, $P=0.018$); there was a tendency towards a lower average daily intake of non-haem iron ($t=1.724$, $P=0.086$) and vitamin C ($t=1.921$, $P=0.057$) for iron depleted children. Low intake of haem iron (<0.71 mg/day) was significantly associated with iron depletion with an odds ratio of 3.0 ($P=0.005$). The proportion of iron depleted children who were given whole cows' milk before 12 months of age was almost double that of iron replete children; multivariate analysis showed that both haem iron intake and age of introduction of cows' milk were independently associated with iron depletion.

Conclusions—The results of this study show that, in young children in developed countries, a lower haem iron intake is a major risk factor for iron

depletion; the introduction of whole cows' milk before 12 months is further confirmed as a risk factor. Parental education on nutrition should now focus on these two aspects of nutrition for infants and young children.

Introduction

Young children, whether in developing or developed countries, are at risk of iron deficiency because rapid growth imposes large iron needs and the bioavailability of iron in the diet of infants is low.^{1,2} Recent studies have shown that iron deficiency may have profound non-haematological consequences, including lower developmental scores and impaired behaviour.^{3,4} Prospective studies in Costa Rica and Chile have demonstrated that the effects of iron deficiency anaemia on intelligence quotient (IQ) may be irreversible.^{5,5}

Adult studies have shown that iron from meats (haem iron) is important in iron nutrition because it may be seven times more readily absorbed than iron from vegetable sources (non-haem iron).⁶ Several factors have been reported to be associated with poor iron status in infants and young children, including low birth weight,⁷ low socioeconomic status,⁸ early introduction of cows' milk (before 12 months),⁹ excessive intake of cows' milk after 12 months,¹⁰ late introduction of solids,^{11,12} and low total iron intake.¹³

We have not been able to find any published studies which have directly measured the intake of haem iron in children in the 12-36 month age group. We tested