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No paternal effect on monozygotic twinning in the Swedish Twin Registry

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Previous research has provided evidence for a genetic effect in monozygotic twinning, indicated by an increased risk for monozygotic women to have monozygotic offspring. However, since the biological mechanism for this trait is unknown, it is not clear if there exists a paternal inheritance. In this study we investigated twin pregnancies in offspring born in 1941–1996 to male twins in the Swedish Twin Registry and population controls born in 1926–1980. In total 4 225 331 offspring, of which 89 286 were twins, were studied. There was neither an increase in the probability for monozygotic men to have like-sexed twin offspring risk ratio (RR = 0.95; 95% CI = 0.77–1.13) nor an increase in the estimated number of monozygotic twin births. Thus, there is no evidence for a paternal effect on monozygotic twinning, suggesting that the gene(s) increasing the liability for division of the embryo are expressed in the mother and not in the fertilised egg.

Keywords: monozygotic twins, multiple pregnancy, risk estimate, genetics, paternal inheritance

Introduction

The etiology of monozygotic twinning is to a large extent unknown and has usually been assumed to be completely random. However, it has been shown that artificially induced ovulation increases the monozygosity rate.[1] Further, we have earlier shown that monozygotic mothers have an increased probability of giving birth to monozygotic offspring in a population-based registry study,[2] indicating that, in addition, genetic effects are of importance for this trait. Support for genetic effects in monozygotic twinning also comes from interview studies where mothers of monozygotic twins report an excess of monozygotic twins among their relatives.[3,4] There are also reports of increased monozygotic twinning rates in selected pedigrees.[5–8] Recent studies suggesting that frequency of twinning is maintained by natural selection again indicate the importance of genetic effects.[9]

The biological mechanism for monozygotic twinning is not known, but there are several suggestions, including abnormalities in zona pellucida or in developmental clocks and development of a discordant cell line, possibly due to skewed X-chromosome inactivation.[10–12] There are therefore two possibilities for how genetic effects for monozygotic twinning could be mediated:

1) via the mother (if the biological mechanism is expressed only in the mother), and
2) via the fertilised egg (if the embryo's DNA is of importance).

In the latter case, paternal inheritance should be evident.

In order to test for possible paternal inheritance in monozygotic twinning we have investigated the offspring of male monozygotic twins from a large population-based twin registry.

Material and methods

This study is based on a linkage of two nationwide Swedish registries: the Swedish Twin Registry,[13] which encompasses data on all twins born in Sweden during the years 1886 to 1991, and the population-based birth registry maintained by Statistics, Sweden. Record linkage identified the male twins and population controls, born 1926 to 1980, to whom children were born in Sweden between 1941 and 1996. In total the linkage yielded 4 225 331 offspring, of whom 89 286 individuals were twins.

The Twin Registry contains information on the sex of all the twins and, for persons born before 1959, zygosity determined on the basis of childhood resemblance.[14] Zygosity diagnoses were verified for 99% of the monozygotic and 92% of the dizygotic twins in a subsample using serological data.[15]

Information from the birth registry includes the year of birth, maternal age and parity, and the

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number of infants in the birth. There is no indication of the zygosity of the offspring in the registry. However, the sexes of the children in the twin pair are known, so an increase in monozygotic offspring will produce an increase in like-sexed twin offspring. The observed numbers of multiple births were compared with the expected numbers, calculated from the rate of multiple births in the total birth registry, stratified by maternal age and parity.

The estimated rate of monozygosity was based on the Weinberg assumption[16] that the number of like-sexed and unlike-sexed dizygotic twins are the same. Thus, the number of monozygotic twins is estimated to be the difference between the total number of twins minus twice the number of unlike-sexed twins. Although the correctness of Weinberg's rule may be questioned,[17] the potential bias for this study is negligible because there is no reason to assume different biases between fathers who are twins and fathers who are singletons.

Results

Table 1 shows the births according to paternal twin type for the cohort born between 1926 and 1958. As can be seen from the table, there is neither an increase in the probability of like-sexed offspring of monozygotic men (RR = 0.95; 95% CI 0.77–1.13) nor an increase in the estimated number of monozygotic twin births. The risk ratio (RR) of 'estimated' to 'expected' numbers of monozygotic births is 0.71. Even in the group of fathers with unknown zygosity (including about 50% monozygotic twins), there is no increase in monozygotic offspring. Thus, there is no evidence for a paternal effect on monozygotic twinning in this cohort.

There is currently no information in the Swedish Twin Registry on the zygosity of men born between 1959 and 1980. The only information available is the sex of the co-twin. Therefore, only unlike-sexed dizygotic twins can be identified. However, monozygotic twins constitute about half of the twins in the group 'unknown zygosity'; thus if there is an increase in monozygotic offspring to monozygotic male twins there should be an excess of like-sexed offspring in this group. As can be seen in Table 2 there is no evidence of a paternal effect on monozygotic twinning in this cohort either (RR = 1.01; 95% CI 0.81–1.21).

In Table 1, dizygotic paternal twin type was not associated with an increased risk of like-sexed twins (RR = 1.06), but in Table 2 such a risk increase reaching formal statistical significance (RR = 1.36) is seen. A possible explanation for this increase could be that dizygotic fathers have an increased risk of having dizygotic offspring. However, risk of dizygotic twinning is easiest detected by an increase in risk of unlike-sexed twin offspring, and since the dizygotic fathers in the cohort born in 1959–1980 display a decreased risk of having unlike-sexed offspring (RR = 0.55, see Table 2) the most probable explanation is that this significant risk increase is a result of multiple testing.

Discussion

This study of over 4 million offspring to men born in 1926–1980 gave no evidence of a paternal effect on monozygotic twinning; that is, fathers who were

Table 1 Observed and expected numbers of births 1941–1996 to Swedish fathers born 1926–1958 who are twins, by twin type

Offspring	Paternal twin type		
	Monozygotic	Dizygotic	Unknown zygosity
Singletons	8038	31055	10037
Twins: like-sexed			
observed	104	450	120
expected	109.6	423.7	133.3
risk ratio	0.95	1.06	0.90
(95% CI)	(0.78–1.15)	(0.97–1.16)	(0.75–1.08)
Twins: unlike-sexed			
observed	70	268	60
expected	61.9	242.0	75.9
risk ratio	1.13	1.11	0.79
(95% CI)	(0.89–1.43)	(0.98–1.25)	(0.61–1.02)
Monozygotic: estimated	34	182	60
Monozygotic: expected	47.7	181.7	57.4
Risk ratio estimated/expected	0.71	1.00	1.05

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Table 2 Observed and expected numbers of births 1941–1996 to Swedish fathers born 1959–1980 who are twins, by twin type

Offspring	Paternal twin type	
	Dizygotic	Unknown zygosity
Singletons	3094	5944
Twins: like-sexed		
observed	66	93
expected	48.6	92.2
risk ratio	1.36	1.01
(95% CI)	(1.07–1.72)	(0.82–1.23)
Twins: unlike-sexed		
observed	12	34
expected	21.8	41.0
risk ratio	0.55	0.83
(95% CI)	(0.32–0.96)	(0.59–1.16)
Monozygotic: estimated	54	59
Monozygotic: expected	26.8	51.2
Risk ratio estimated/expected	2.01	1.15

monozygotic twins had no increased probability of having like-sexed twin offspring.

The indications of a genetic transmission of monozygotic twinning in women in previous studies,[2–4] together with the lack of evidence of paternal effect in monozygotic twinning suggest that the gene(s) increasing the liability for division of the embryo are expressed in the mother and not in the feritilised egg. The data are congruent with the hypothesis that one cause of monozygotic twinning is due to an inherited abnormality of the zona pellucida in the mothers.[11] On the other hand, hypotheses suggesting an effect of skewed X-chromosome inactivation or abnormalities in cell-to-cell connections allowing cells to separate before implantation and placentation[18] would involve the DNA of the foetus, for which there is no evidence in the data. Other possible explanations of the results could be genomic imprinting.[10]

It should be noted that there was no significant effect for dizygotic fathers having unlike-sexed twin offspring, a result which would have been expected if there were a paternal effect on dizygotic twinning. Earlier research has shown systematic evidence of a genetic effect expressed in women,[2,3,19,20] most probably due to a genetic predisposition for multiple ovulation.[21,22] However, there have been sporadic reports of a paternal effect, primarily from interview studies of fathers of dizygotic twins reporting an excess of dizygotic twins among their relatives.[3] Because our study uses a population-based registry study we suspect that earlier reports of a paternal effect on dizygotic twinning are due to recall bias.

We conclude that there is no evidence for a paternal effect on twinning, neither monozygotic nor dizygotic, and that the search for biological causes for these phenotypes should concentrate primarily on the mothers.

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