The Correlation of Fecundability Among Twins: Evidence of a Genetic Effect on Fertility?

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Background. Numerous rare genetic conditions are known to influence fecundability in both males and females. It is less clear to what extent more subtle genetic differences influence fecundability on a population level.
Methods. In 1994 a population-based survey was conducted among Danish twins born 1953–1982. Fecundability was assessed as the waiting time to pregnancy at the first attempt to achieve a pregnancy.
Results. The reported time to pregnancy for males was slightly shorter than for females but there were no sex differences in intrapair similarity. We found an intrapair correlation in time to pregnancy for 645 monozygotic twin pairs (r = 0.22; 95% confidence interval = 0.12 to 0.32), but no intrapair correlation for 826 like-sex dizygotic twin pairs (r = 0.00; 95% confidence interval = −0.09 to 0.10).
Conclusions. The correlation in time to pregnancy for monozygotic twins suggests genetic factors, although similarities in reporting behaviors could also be contributing to the correlation. The lack of correlation in time to pregnancy for dizygotic twins indicates that possible genetic factors of importance for fecundabililty are acting nonadditively. Hence, it may prove difficult to identify specific gene variants that influence fecundability on a population level if their effects depend on gene-gene interactions.
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Key words: fecundability, fertility, twins, genetics, gene-gene interaction.

Infertility and subfecundity are major health problems for which a number of determinants on a population level have been identified (*eg*, smoking, medicine, and sexually transmitted diseases[1,2] for females, and infections [especially mumps], heat exposure, and possibly environmental estrogen for males).[3] Rare genetic factors that affect fertility and fecundity have long been known (*eg*, Turner's syndrome and Klinefelter's syndrome). Newer research indicates that *de novo* microscopic deletions on the Y chromosome may be a rather common cause of male infertility.[4,5,6]

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It may seem counterintuitive to study genetic factors influencing fertility, because a genetic factor associated with infertility cannot naturally be transmitted to the next generation (as in the old joke "Celibacy runs in families"). However, the level of fecundability could have a genetic component, in that very high fecundity may not have been optimal from an evolutionary perspective.

Fisher's[7] 1930 Fundamental Theorem of Natural Selection predicts that natural selection tends to remove additive genetic variation in traits or behaviors related to reproductive success (so-called fitness traits). Of course, other natural processes (*eg*, mutations) can reintroduce genetic variance as natural selection washes it out. But in terms of natural selection, if a gene variant is affecting a fitness trait over generations it will either be selected against (if the effect is negative) or it will go to fixation, *ie*, almost all in the population will have the gene variant (if the effect is positive). However, selection over generations does not affect nonadditive genetic effects, *ie*, gene-gene interactions. This means that nonadditive genetic effects are a source of similarity within a generation (siblings) but not over generations (parents and offspring). A simple illustration of nonadditive genetic effects is a rare recessive genetic trait (*eg*, cystic fibrosis). Such traits rarely co-occur across generations (*ie*, parent and offspring), but 25% of the siblings of an affected person will also be affected.

Twin studies can help to disentangle the relative contributions of genetic and environmental factors on trait variation. If a fitness trait like fecundability is determined solely by nonfamily environmental factors and multiple gene-gene interactions, a correlation for the trait within monozygotic twin pairs can be expected, whereas there should be negligible correlation within dizygotic twin pairs.[8] To test this prediction we used a survey among Danish twins who were born in the period 1953–1982, and who are identified in the population-based Danish Twin Registry.

Because of contraception, the total number of children is not a good measure of the ability to conceive. Therefore in this study we assessed fecundability as waiting time to pregnancy, *ie*, the number of months it takes a couple to achieve a clinically recognized pregnancy when practicing unprotected intercourse. We included both males and females in the study; we also report on the waiting time to pregnancy for the male twins and compare them with the previously published data for female twins in the survey.[9]

Methods

The twin survey was conducted among all twins born in the period 1953–1982 who are identified in the Danish Twin Registry (corresponding to 20,888 twin pairs). This twin population has previously been described in detail.[9,10] In 1994, these twins received a seven-page questionnaire comprising a broad range of health-related questions. This project has been approved by the Danish Scientific Ethical Committee. A total of 24,346 twins age 18+ years returned the questionnaire. The response rate was 89%, corresponding to 79% of the overall Danish twin population (not all Danish twins from these cohorts completed the intake assessment in 1991–1992). The zygosity of like-sex twins had previously been established based on questions about similarity, a method that has been shown to have a misclassification rate of less than 5% when compared with the results from blood group determinants and genetic markers.[11]

To reduce the influence of health services or lifestyle changes based upon past reproductive experience, fecundability was measured as the first attempt to achieve a pregnancy.[12] Calendar year and hence age at first attempt were included. The following answer categories were given: never tried to become pregnant; became pregnant despite the use of contraception; became pregnant after *x* months (*ie*, waiting time to pregnancy); stopped trying after *x* months; still trying and have now been trying for *x* months. Respondents were asked to choose from the following time intervals: less than 2 months (corresponds to "within 2 cycles"), 2–4 months, 5–9 months, 10–17 months and 18+ months. These intervals were chosen to avoid the typical digit preferences (3, 6, 12 and 18 months). The last category (18+ months) was not further divided, because infertility treatment can interfere with longer waiting times.

We analyzed time to pregnancy only for responders who had valid and consistent answers to all relevant questions. Among the responders there were 645 monozygotic pairs and 826 like-sex dizygotic pairs with a valid time to pregnancy for both members of the pair. Of the 645 monozygotic pairs, 252 (39%) were males, whereas the corresponding number for like-sex dizygotic twins was 339 out of 826 (41%). We calculated polychoric correlations for time to pregnancy within twin pairs. To obtain a reasonable size in all cells we used the categories <2 months, 2–9 months and 10+ months for the intrapair comparisons. We also tested the intrapair association with a χ^2 test for independence.

Results

Tables 1 and 2 show the outcome of male twins' first attempt to have a child, stratified by zygosity. We previously reported similar tables for female twins and singletons.[9] To make the male data directly comparable with the female data we have restricted Table 2 to the birth cohorts 1953–1966, omitting the youngest cohorts (with very few pregnancy attempts). The overall patterns were very similar for men and women with a few exceptions. As expected, men were 2 years older than women at first attempt to have a child (26.8 years *vs* 24.8 years). Fewer men than women reported that a pregnancy had been achieved despite the use of contraception, and a bigger proportion of male respondents had missing values. The male twins reported slightly shorter time to pregnancy compared with the female twins; the cumulative distribution of time to pregnancy for men was 60% by <2 months, 78% by <5 months, 88% by <10 months, 93% by <18 months compared with 55%, 73%, 85% and 90%, respectively, for women. Birth control–failure pregnancies were included in a subanalysis as having time to pregnancy less than 2 months. The similarity in time to pregnancy for all zygosity groups persisted after this extension.

Tables 1 and 2 show that, as in female twins,[9] outcome of the men's first attempt to have a child did not differ among monozygotic, dizygotic like-sex, and dizygotic unlike-sex twins. Table 1 illustrates that it is the "never tried" and missing data (especially among the youngest responders) that is responsible for the attrition in sample size when studying intrapair similarity in time to pregnancy.

We found an intrapair correlation of time to pregnancy for the monozygotic twin pairs (r = 0.22; 95% confidence interval [CI] = 0.12 to 0.32), whereas there was no intrapair correlation for the dizygotic like-sex twin pairs (r = 0.00; CI = −0.09 to 0.10) (Table 3). The correlations were nearly identical for men and

TABLE 1. Frequency (%) of Outcomes of First Attempt to Have a Child Among Danish Male Twins (Birth Cohort: 1953–1976)

Age at Interview	Zygosity*	Pregnancy Achieved	Still Trying	Gave up Trying	Despite Contrac.†	Never Tried	Missing Data	Total (N)
18–24	DZ unlike-sex	2.1	0.8	0.3	1.2	43.4	52.2	859
	DZ like-sex	2.6	0.9	0.3	0.9	45.8	49.5	1,092
	MZ	2.1	0.5	0.1	0.9	40.0	56.5	1,022
25–29	DZ unlike-sex	21.4	3.0	0.2	2.5	38.2	34.7	845
	DZ like-sex	21.0	3.3	0.3	3.7	38.4	33.3	952
	MZ	25.6	3.6	0.1	3.9	37.8	28.8	687
30–34	DZ unlike-sex	46.4	3.2	0.2	4.3	21.5	24.3	957
	DZ like-sex	49.1	4.0	0.3	3.7	19.6	23.3	1,003
	MZ	45.3	5.5	0.9	4.6	19.9	23.7	633
35+	DZ unlike-sex	54.9	2.6	1.4	3.6	11.9	25.6	1,034
	DZ like-sex	55.1	2.8	0.9	4.1	10.9	26.3	1,375
	MZ	59.1	2.3	1.6	4.1	9.6	23.2	798
Total (N)		3,644	292	63	345	3,110	3,803	11,257‡

DZ = dizygotic; MZ = monozygotic.
* Zygosity of male twin study respondent.
† Pregnant despite contraception.
‡ Not included in the table are 408 twins of unknown zygosity.

women both for monozygotic twins (0.20 *vs* 0.24) and for dizygotic twins (0.01 for both sexes).

In our analyses we also investigated whether these intrapair correlations may have been affected by a potential association between the age at first attempt at pregnancy and the waiting time to pregnancy. For this purpose we estimated the intrapair correlations using the bivariate ordered probit models[13] with the following explanatory variables of the waiting time to pregnancy: sex, age at first attempt, and age at first attempt squared. The analyses revealed a modest influence of age at first attempt on the waiting time for dizygotic twins, but no substantial influence for monozygotic twins. The estimation of the intrapair correlation was virtually unchanged after this age pattern was included in the estimation. We also investigated whether the results for both the age pattern and the intrapair correlation were sensitive to the combination of waiting-time categories in Table 3 (three categories *vs* five categories originally). It turned out that neither estimate was affected by this reduction in number of categories.

We also note that, when the "10+ months" category is deleted from Table 3, the monozygotic twin correlation drops. In other words, much of the similarity for monozygotic twins seems to come from those monozygotic twin pairs in which at least one had a very long waiting time to pregnancy. We will further develop the implications of that part of the pattern in future research.

Discussion

In this study we assessed fecundability using waiting time to pregnancy on the first attempt to achieve a pregnancy. Time to pregnancy has been shown to be a sensitive and valid measure of fecundability on a population level even for pregnancies occurring up to 20 years earlier,[14] although reporting is more reliable with shorter duration of recall. Previous studies of men's reports of time to pregnancy have indicated that men's time-to-pregnancy data on a population level are of comparable quality with those of women, with closely comparable distributions and the same degree of digit preferences.[15] In our study we have eliminated the digit preference problem by using categories, and we observed that the distribution of time to pregnancy as reported by the male twins was shifted slightly towards shorter lengths. However, the correlations within twin pairs were similar for men and women both for monozygotic and dizygotic twins. The probit models suggested that the correlations were not affected to any substantial degree by age at first attempt to obtain a pregnancy.

TABLE 2. Distribution (%) of Age at the First Attempt to Have a Child for Danish Male Twins (Birth Cohort: 1953–1966)

	<21 Years	21–25	26–30	31+	Mean	SD	Total
Pregnant despite contraception excluded							
All twins	4	34	46	16	26.8	3.8	3,368
DZ unlike-sex	4	33	47	16	26.9	3.8	1,130
DZ like-sex	4	35	46	15	26.8	3.8	1,372
MZ	4	35	46	15	26.7	3.8	866
Pregnant despite contraception included							
All twins	4	35	46	15	26.7	3.8	3,521
DZ unlike-sex	4	33	46	16	26.7	3.8	1,178
DZ like-sex	4	35	46	15	26.7	3.8	1,433
MZ	5	35	45	15	26.6	3.8	910

DZ = dizygotic; MZ = monozygotic.

TABLE 3. Waiting Time to Pregnancy for Danish Twins Born 1953–1976*

	Twin 2		
	<2 months	2–9 months	10+ months
Monozygotic (N = 645 pairs)†			
Twin 1			
<2 months	210 (33%)	94 (15%)	45 (7%)
2–9 months	86 (13%)	48 (7%)	39 (6%)
10+ months	52 (8%)	36 (6%)	35 (5%)
Dizygotic like-sex (N = 826 pairs)‡			
Twin 1			
<2 months	240 (29%)	112 (14%)	78 (9%)
2–9 months	123 (15%)	80 (10%)	37 (5%)
10+ months	86 (10%)	44 (5%)	26 (3%)

* The calculations include pairs with valid waiting time to pregnancy for both members of the twin pairs. Twins still trying to achieve a pregnancy and twins who have stopped trying were also included, if they had tried for 10 months or more.
† Polychoric correlation coefficient = 0.22 (95% CI = 0.12 to 0.32).
‡ Polychoric correlation coefficient = 0.00 (CI = −0.09 to 0.10).

We found a modest correlation (r = 0.22) of time to pregnancy for monozygotic twins, whereas there was no correlation for dizygotic twins (r = 0.00). Comparing the proportions in Table 3, the difference in distribution between monozygotic and dizygotic twins seems slight, but it is still detectable in the correlation analyses and in the independence tests (not shown).

When interpreting the size of the correlation one should bear in mind that fecundability is a couple characteristic. The partners of twins greatly affect the fecundability estimates, especially in cases where fertile twins have infertile partners. Also, any nondifferential misclassification is likely to reduce the twin similarity. Thus, it seems likely that there is a considerable familial component to variation in fecundity, because we are able to detect a correlation in monozygotic twins despite the partner effect and potential misclassification. However, if monozygotic twins have more similar reporting behavior than dizygotic twins, this could also contribute to the observed correlation pattern.

Other studies have tried to assess the genetic component of variation in human fertility. One example is the classic paper by Fisher[7] (1930) in which he showed 40% heritability in completed family size among a sample of British aristocrats, although Fisher's study could not disentangle a common environment from genetic factors. A study of U.S. twins reared apart showed correlations for completed family size for both monozygotic and dizygotic twins, but the sample size was small.[16] Rodgers and Doughty (2000)[17] estimated that in a contemporary U.S. population about a third of the variation in completed fertility at early ages could be attributed to genetic factors.

In modern societies there can be a poor correlation between final family size and fertility because of contraception and infertility treatment. Male fecundability may also be estimated through sperm analyses; such studies have also suggested the importance of genetic factors in male fertility. A British study identified brothers of men with an abnormal sperm count who attended a subfertility clinic and whose partners had no major factors that might reduce their fertility. These brothers had sought medical advice for childlessness more often than brothers of men who attended vasectomy clinics.[18] A French study found evidence that brothers of infertile men had lower sperm count, poorer mobility and fewer normal forms.[19] Based on such studies we expected to find at least a small correlation in time to pregnancy for dizygotic male twins who are genetically like ordinary siblings. It is possible that the reason for not detecting any intrapair similarity for time to pregnancy for dizygotic twins in this study was lack of power or misclassification. However, another possibility is that the nature of the genetic influence on fecundability involves a specific configuration of genes, *ie*, a certain combination of alleles in which all alleles are necessary, but as single alleles without the other specific alleles they are of no importance for the trait. Lykken *et al.*[20] described the process of "emergenesis," by which genetic influences require a polygenic configuration of alleles. In such a circumstance, monozygotic twins are expected to have substantial twin correlations, whereas dizygotic twins (and other kinship levels) will have correlations of zero, exactly the pattern observed in the current data. However, past brother (full sibling) correlations reviewed above are not consistent with an emergenesis interpretation (although sperm mobility, receiving medical advice and time to pregnancy are very different measures of fertility). Obviously, resolving the question of how genetic influences are expressed will require additional data.

The correlation of time to pregnancy observed among monozygotic twins can arise because of genetic factors, although a possible similarity in reporting behavior unrelated to genetic factors could also contribute to this pattern. The lack of correlation in time to pregnancy among dizygotic twins suggests that the possible genetic factors of importance to time to pregnancy are acting nonadditively, *ie*, through gene-gene interactions. To identify polymorphisms that interact with other genes is logistically and analytically far more complex than identifying additive genetic factors. This suggests that identifying specific gene variants that influence fecundability on a population level may prove difficult.

Appendix

The bivariate (ordered) probit model used in this paper estimates the correlation of a latent bivariate normal distribution that generates the observed trait values for twin one and two within a twin pair. The bivariate (ordered) probit model differs from the polychoric correlations in that it accounts for different mean levels of a dichotomous or ordered trait that is attributable to the influence of observed individual or pair-specific characteristics on a trait value such as age or education. The heritabilities are therefore correctly estimated even if individual or pair-specific observed covariates, such as age or education, affect the mean realization of the trait value (for further discussion, see Kohler and Rodgers, 1999[13]).

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