Fecundability of Female Twins

Kaare Christensen,[1] Olga Basso,[2] Kirsten O. Kyvik,[1] Svend Juul,[2] Jesper Boldsen,[2] James W. Vaupel,[1] and Jørn Olsen[2]

Animal studies have shown evidence of prenatal hormonal interaction between unlike sexed fetuses, including reduced fertility among females. We evaluated whether the fecundability of female twins is different from that of singletons and whether it differs according to the sex of the co-twin. The study was based on a questionnaire survey of 12,681 female twins born in the period 1953–1976 and an interview survey of 760 female controls born in the period 1953–1966, both in Denmark. Outcome of the first try ever to become pregnant (pregnant, still trying, stopped trying, pregnant despite contraception, and never tried) and the waiting time to pregnancy distribution did not differ among monozygotic, dizygotic same sexed, and dizygotic unlike sexed twins. More twins had a waiting time of less than 2 months, compared with singletons. This difference probably reflects an artifact due to the data collection method, because it disappeared when the cutoff point was changed to include 2 months for singletons, and we found no difference for longer waiting times. Hence, we found no increase in fecundability for twins compared with singletons, nor any reduced fecundability among female twins from unlike sexed pairs. (Epidemiology 1998;9:189–192)

Keywords: fecundability, fertility, hormones, sex, twins, zygosity.

In highly industrialized countries, most couples want to control and time their pregnancies, and the use of effective contraception is widespread. Usually, couples want a small family, and even couples with low ability to conceive will often be able to produce the one child or two children they want. Therefore, in most industrialized countries, the number of children does not measure the ability to conceive (fecundability). An estimate of fecundability is waiting time to pregnancy, that is, the number of months or cycles it takes a couple to achieve a clinically recognized pregnancy when practicing unprotected intercourse.

The focus of the present paper is the fecundability of female twins, which could be expected to differ considerably from that of other women for several reasons. Approximately one-third of all female twins are from unlike sexed twin pairs, that is, these females shared the uterus with a male fetus, and hence they were potentially exposed to male hormones *in utero*. This exposure has been suggested as the mechanism for the observed masculinization of certain physiologic and psychological traits in females from unlike sexed twin pairs.[1–3] Prenatal exposure to exogenous hormones is generally suspected to be of importance for later life conditions in humans, and it has been shown that women prenatally exposed to diethylstilbestrol have an increased risk not only of vaginal and cervical cancer but also of reproductive difficulties, including infertility.[4] Furthermore, in cattle, a female twin fetus with a male co-twin is most often sterile, the so-called freemartin phenomenon.[5] In 1844, Simpson noticed that in humans the number of offspring of female twins is not affected by the sex of the co-twin.[6] It is not known, however, whether female twins from unlike sexed pairs have different fecundability, since, as mentioned, even large differences might not correlate with fertility.

It is well established that dizygotic twinning runs in families among females.[7,8] A recent study by Lichtenstein *et al*[9] indicated that monozygotic twins also tend to aggregate in families. To be a twin mother can be regarded as an indication of high fecundability, at least in the case of dizygotic twinning, which represents ovulation, fertilization, and nidation of two eggs. If being a twin mother has a genetic component and represents high fecundability, it could be expected that female twins have higher fecundability than other women. For female twins from unlike sexed pairs, this effect would act in the opposite direction of the hypothesized influence of male hormones.

The aim of the present paper was to evaluate two hypotheses: (1) female twins from unlike sexed pairs

From the [1]Danish Twin Registry, Odense University Medical School, Odense, and [2]The Danish Epidemiology Science Centre/Department of Epidemiology and Social Medicine, Aarhus University, Aarhus, Denmark.

Address correspondence to: Kaare Christensen, Odense University Medical School, Winslowparken 17, DK-5000 Odense C, Denmark.

Supported by Sygekassernes Helsefond (Grant 11/209-93). The activities of the Epidemiology Science Centre is funded by a grant from the Danish National Research Foundation. Olga Basso is funded by the Danish Research Academy (Grant 1995-145-0057).

Submitted February 24, 1997; final version accepted October 10, 1997.

have reduced fecundability compared with other groups of female twins; (2) female twins, in particular from like sexed dizygotic pairs, have higher fecundability than singletons. The study was based on a questionnaire survey among 12,681 Danish female twins born between 1953 and 1976. We used the Danish component of a collaborative European project on fecundability to obtain fecundability data from the background population.

Methods

The twin survey was conducted among all twins born in the period 1953–1982 who are identified in the Danish Twin Registry (20,888 twin pairs). This twin population has previously been described in detail.[10] In 1994, these twins received a seven-page questionnaire comprising a broad range of health-related questions. The response rate was 89%, corresponding to 79% of the Danish twin population. A total of 12,681 women 18 years of age or older returned the questionnaire. The zygosity of like sexed twins had previously been established on the basis of questions about similarity, a method that has shown a misclassification rate of less than 5% compared with the results from blood group determinants and genetic markers.[11]

To reduce the influence of health services or life-style changes based upon past reproductive experience, the fecundability questions focused on 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; stopped trying after *x* months; still trying and have now been trying for *x* months. Number of months had to be selected from the following intervals: <2 months, 2–4 months, 5–9 months, 10–17 months, and ≥18 months. These intervals were chosen to avoid the digit preferences (3, 6, 12, and 18 months) that were present in the comparison group. The last category (≥18 months) was not further divided, since infertility treatment can interfere with longer waiting times.

The European Study of Infertility and Subfecundability was based upon random sampling and personal interviewing of women born between 1946 and 1966 in seven regions in five countries in Europe.[13] In Denmark, Aarhus was the sample frame; of 1,184 women, 1,028 were interviewed (86.8%). The interviews were conducted by specially trained female interviewers in August 1991. The main information collected concerned reproductive history, waiting time to pregnancy, and other questions related to reproduction. Waiting time to pregnancy was assessed on a continuous scale using the question: "How many months did it take you to become pregnant, that is, how many months did you have sexual intercourse without doing anything to avoid pregnancy?" The interviewers probed only when a woman was reluctant to answer, encouraging her to give her best estimate of the waiting time. The present study used only information related to the waiting time to the first pregnancy, and it was restricted to the 760 women from the birth cohorts 1953–1966 to make it comparable with the corresponding twin cohorts.

Results

Table 1 shows the outcome of first try ever to become pregnant, stratified for zygosity and age at the survey for all female twins. The patterns were very similar for monozygotic, dizygotic like sexed, and dizygotic unlike sexed twins in all age strata. A total of 4,837 female twins reported a waiting time to pregnancy.

As seen in Table 2, the singletons were on average 1.1 year younger than the twins at the first try ever to become pregnant. The Mantel-Haenszel analysis for stratified data, however, showed that control of age did not change any of the effect measures and therefore did not confound the analyses of waiting time to pregnancy. We obtained similar results when the analysis was restricted to women who first attempted to become pregnant at 20–34 years or 20–29 years of age.

In Table 3, the waiting time to pregnancy distribution, is given only for the 1953–1966 cohorts to make the twin and singleton cohorts comparable. Nevertheless, the distribution was nearly unchanged when we

TABLE 1. Frequency (%) of Outcomes of First Try Ever to Become Pregnant among Danish Twins (Birth Cohort: 1953–1976)

Age (Years) at Survey and Zygosity*	Pregnancy Achieved	Still Trying	Gave Up Trying	Pregnant Despite Contraception	Never Tried	Missing Data†	Total (N)
18–25							
DZ unlike sexed	4.9	1.0	0.0	3.2	51.1	39.8	963
DZ like sexed	4.6	0.7	0.4	2.8	51.1	40.5	1,134
MZ	3.8	1.7	0.2	2.1	53.5	38.8	1,248
26–29							
DZ unlike sexed	31.8	4.6	0.6	5.7	31.2	26.0	995
DZ like sexed	31.5	5.2	0.4	5.8	32.1	25.0	1,034
MZ	32.4	4.2	0.6	4.0	33.9	24.9	935
30–34							
DZ unlike sexed	59.4	3.8	1.0	7.2	11.6	17.2	1,090
DZ like sexed	58.6	3.8	0.4	6.8	12.0	18.3	1,168
MZ	58.4	2.4	1.0	6.8	14.7	16.7	819
≥35							
DZ unlike sexed	60.4	1.6	1.6	8.8	7.3	20.3	1,221
DZ like sexed	61.8	2.1	1.9	8.5	8.8	17.0	1,119
MZ	63.9	2.0	1.1	8.2	7.7	17.1	648
Total (N)	4,744	340	93	713	3,321	3,163	12,374‡

* DZ = dizygotic; MZ = monozygotic.
† Subjects who skipped fertility questions or did not remember.
‡ 307 twins of unknown zygosity are not included in the table.

TABLE 2. Distribution (%) of Age at First Try Ever to Become Pregnant for Danish Twins and Singletons (Birth Cohort: 1953–1966)

	% at Age (Years)						
	<21	21–25	26–30	≥31	Mean	(SD)	Total
	A. Pregnant despite contraception excluded						
All twins	12.7	45.8	35.4	6.2	24.8	(3.7)	4,196
DZ unlike sexed	13.2	46.0	35.1	5.7	24.7	(3.7)	1,566
DZ like sexed	13.1	46.5	33.6	6.8	24.8	(3.7)	1,554
MZ	11.2	44.4	38.3	6.0	24.9	(3.6)	1,076
Singletons	24.3	42.3	29.5	3.9	23.7	(3.9)	383
	*B. Pregnant despite contraception included**						
All twins	13.3	46.1	34.4	6.2	24.7	(3.7)	4,538
DZ unlike sexed	13.7	46.4	34.1	5.8	24.7	(3.7)	1,696
DZ like sexed	13.7	47.1	32.5	6.7	24.7	(3.7)	1,681
MZ	12.0	44.2	37.7	6.1	24.8	(3.6)	1,161
Singletons	26.6	41.4	28.1	3.9	23.6	(3.9)	459

* The discrepancies with the totals given in Table 3 are due to missing values in reporting age at the first try for those pregnant despite contraception.

included the 1967–1976 cohorts for the twins and the 1946–1952 cohorts for the singletons. There was little difference in the distribution of waiting times to pregnancy among monozygotic, dizygotic like sexed, and dizygotic unlike sexed twins. Hence, we pooled these twin groups in the following analyses. In the comparison of waiting time to pregnancy for twins and singletons, the only substantial difference was that more twins, compared with singletons, had a waiting time of less than 2 months: 54.7% (2,297 of 4,196) *vs* 44.6% (171 of 383), a difference of 10.1% [95% confidence interval (CI) = 4.9%–15.3%]. Including the singletons who reported a waiting time of 2 months in the group of fast conceivers changed the singleton proportion to 55.9%, and we observed little difference for longer waiting times. Including women who became pregnant despite the use of contraception as fast conceivers did not change the results, except that it reduced the difference between twins and singletons regarding the proportion who had a waiting time of less than 2 months: twins 59.9% (2,842 of 4,741) *vs* singletons 54.0% (249 of 461), a difference of 5.9% (95% CI = 1.1%–10.7%).

TABLE 3. Cumulative Frequency (%) of Waiting Time to Achieved Pregnancy for Danish Twins and Singletons (Birth Cohort: 1953–1966)

	% at Months of Waiting Time				
	<2	<5	<10	<18	Total
	A. Pregnant despite contraception excluded				
All twins	54.7	73.0	84.5	90.4	4,196
DZ unlike sexed	54.5	71.9	83.7	90.4	1,566
DZ like sexed	55.1	73.4	85.6	90.9	1,554
MZ	54.5	73.9	84.1	90.0	1,076
Singletons	44.6	70.2	83.3	90.6	383
	B. Pregnant despite contraception included				
All twins	59.9	76.1	86.3	91.5	4,741
DZ unlike sexed	59.9	75.2	85.6	91.5	1,777
DZ like sexed	60.4	76.5	87.3	91.9	1,760
MZ	59.3	76.7	85.8	91.0	1,204
Singletons	54.0	75.3	86.1	92.2	461

Discussion

This study found no substantial evidence supporting the hypotheses that the fecundability of female twins is different from that of singletons and differs according to the sex of the co-twin. Our study design depends on recalling waiting time to pregnancy dating back in time 0–13 years, using different instruments among twins and singletons. At the group level, however, waiting time to pregnancy has been shown to be a reproducible measurement within broad categories, even with a recall of 10–15 years or more.[14] Furthermore, various instruments (interviews and questionnaires) used to assess waiting time to pregnancy have been shown to correlate with differences in population sperm counts.[15]

Women who become pregnant despite the use of contraception are difficult to classify in terms of fecundability, as they probably represent individuals using irregular and/or less effective contraception as well as some women with high fecundability. Therefore, we excluded these women from the initial analysis and classed them with the group with a waiting time less than 2 months in a subsequent analysis, which yielded similar results.

Other factors could affect the waiting time distributions; female twins could represent two groups: a group of "natural twins" with high fecundability, and a group of "iatrogenic twins" (after infertility treatment) with low fecundability. Also, the population selected for sampling singletons could differ in fecundability compared with the rest of Denmark. A further limitation is illustrated in Table 1, which shows that the younger cohorts skipped the fecundability part of the questionnaire; that section may have been considered irrelevant, since these women had not yet started their reproductive career. Finally, a general problem is that fecundability is a function of a couple and not only of the woman. Even the most fecund woman will have ≥18 months waiting time if her spouse is sterile. The male component decreases our power to detect differences between the various groups. Nevertheless, the size of the study allows us to detect major differences, and there is no reason to believe that zygosity of twins is related to selecting spouses with different fecundability levels. Unfortunately, no data on smoking or other environmental exposures were available, and the results therefore could be confounded by these factors.

The influence of prenatal hormone exposure on morphologic, physiologic,

and behavioral characteristics has been extensively studied in rodents.[16] Studies have shown that the intrauterine position of male and female fetuses affects hormone levels, that is, female fetuses located *in utero* between two males have higher levels of male hormone in the blood and a more masculine growth pattern than female fetuses placed between two other females.[17,18] Various studies indicate that male hormones are able to permeate the placenta in animals and humans, and therefore, hormone transfer probably occurs in human unlike sexed twins.[3,19] Any effect on the fecundability of female twins from unlike sexed pairs could not, however, be detected in the present study.

Several studies have indicated the importance of genetic factors in the recurrence of giving birth to dizygotic twins.[8,9,20,21] Giving birth to dizygotic twins can be regarded as an indication of high fecundability, and some evidence is present that dizygotic twinning reflects a high rate of multiple ovulation.[22,23] Hence, if being a twin mother has a genetic component and represents high fecundability, it could be expected that female twins, at least from dizygotic pairs, have higher fecundability than singletons.

Indirect studies of fecundability, such as studies of waiting time to pregnancy after marriage, suggest that mothers of twins have high fecundability,[24–27] but these studies depend heavily upon comparable family planning. The only difference observed in the present study was that more twins, compared with singletons, had a waiting time to pregnancy of less than 2 months. This difference disappeared, however, when the cutoff point was changed to include 2 months for singletons, and no differences were observed for longer waiting times. An expected shift in the entire waiting time to pregnancy distribution for twins was not seen, and it seems most likely that the one observed difference between twins and singletons was an artifact due to the method of data collection.

Acknowledgments

We are grateful to Henning Beck-Nielsen and Anders Green for their help in establishing the twin population.

References

1. McFadden D. A masculinizing effect on the auditory systems of human females having male co-twins. Proc Natl Acad Sci USA 1993;90:11900–11904.
2. Resnick SM, Gottesman II, McGue M. Sensation seeking in opposite-sex twins: an effect of prenatal hormones? Behav Genet 1993;23:323–329.
3. Miller EM, Martin N. Analysis of the effect of hormones on opposite-sex twin attitudes. Acta Genet Med Gemellol (Roma) 1995;44:41–52.
4. Senekjian EK, Potkul RK, Frey K, Herbst AL. Infertility among daughters either exposed or not exposed to diethylstilbestrol. Am J Obstet Gynecol 1988;158:493–498.
5. Kahn MZ, Foley GL. Retrospective studies on the measurements, karyotyping and pathology of reproductive organs of bovine freemartins. J Comp Pathol 1994;110:25–36.
6. Moir JC. Are females born co-twin with males sterile? BMJ 1949;1:69–70.
7. Lewis CM, Healey SC, Martin NG. Genetic contribution to DZ twinning. Am J Med Genet 1996;61:237–246.
8. Meulemans WJ, Lewis CM, Boomsma DI, Derom CA, Van den Berghe H, Orlebeke JF, Vlietinck RF, Derom RM. Genetic modelling of dizygotic twinning in pedigrees of spontaneous dizygotic twins. Am J Med Genet 1996;61:258–263.
9. Lichtenstein P, Olausson PO, Källén AJB. Twin births to mothers who are twins: a registry based study. BMJ 1996;312:879–881.
10. Kyvik KO, Green A, Beck-Nielsen H. The new Danish twin register: establishment and analysis of twinning rates. Int J Epidemiol 1995;24:589–596.
11. Hauge M. The Danish Twin Register. In: Mednick SA, Baert AE, Backman BP, eds. Prospective Longitudinal Research: An Empirical Basis for the Primary Prevention of Psychosocial Disorders. London: Oxford University Press, 1981;218–221.
12. Olsen J. Options in making use of pregnancy history in planning and analysing studies of reproductive failure. J Epidemiol Community Health 1994;48:171–174.
13. Basso O, Olsen J, Bisanti L, Juul S, Boldsen J, and the European Study Group on Infertility and Subfecundity. Are seasonal preferences in pregnancy planning a source of bias in studies of seasonal variation in reproductive outcomes? Epidemiology 1995;6:520–524.
14. Joffe M, Villard L, Li Z, Plowman R, Vessey M. A time to pregnancy questionnaire designed for long term recall: validity in Oxford, England. J Epidemiol Community Health 1995;49:314–319.
15. Joffe M. Decreased fertility in Britain compared to Finland. Lancet 1996; 347:1519–1522.
16. Vom Saal FS. Sexual differentiation in litter-bearing mammals: influence of sex of adjacent fetuses in utero. J Anim Sci 1989;67:1824–1840.
17. Vom Saal FS, Bronson FH. Variation in length of the estrous cycle in mice due to former intrauterine proximity to male fetuses. Biol Reprod 1980;22: 777–780.
18. Kinsley C, Miele J, Wagner CK, Ghiraldi L, Broida J, Svare B. Prior intrauterine position influences body weight in male and female twins. Horm Behav 1986;20:201–211.
19. Meulenberg PMM, Hofman JA. Maternal testosterone and fetal sex. J Steroid Biochem Mol Biol 1990;39;1:51–54
20. Derom R, Orlebeke J, Eriksson J, Thiery M. The epidemiology of multiple births in Europe. In: Keith LG, Papiernick E, Keith DM, Luke B, eds. Multiple Pregnancy: Epidemiology, Gestation and Perinatal Outcome. New York: Parthenon, 1995;145–162.
21. Boomsma DI, Frants RR, Bank RA, Martin NG. Protease inhibitor (Pi) locus, fertility and twinning. Hum Genet 1992;89:329–332.
22. Martin NG, Krester DM, Robertson DM, Osborne J, Chenevix-Trench G, Burger HG. Elevation of follicular phase inhibin and luteinizing hormone levels in mothers of dizygotic twins suggests nonovarian control of multiple ovulation. Fertil Steril 1991;56:469–474.
23. Martin NG, Shanley S, Butt K, Osborne J, O'Brien G. Excessive follicular recruitment and growth in mothers of spontaneous dizygotic twins. Acta Genet Med Gemellol (Roma) 1991;40:291–301.
24. Allen G, Schacter J. Ease of conception in mothers of twins. Soc Biol 1971;18:18–27.
25. Hägberg U, Wall S. Secular trends of twinning rate in Sweden. J Biosoc Sci 1992;24:487–496.
26. MacGillivray I, Campbell DM, Thompson B, eds. Twinning and Twins. London: John Wiley and Sons, 1988.
27. Gabler S, Voland E. Fitness of twinning. Hum Biol 1994;66:699–713.