Fecundability of Female Twins

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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 of only 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 twins 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.3–5 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 al9 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

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

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 cate-
gories were given: never tried to become pregnant; be-
came 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 follow-
ing 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 inter-
viewing 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 con-
ducted by specially trained female inter-
viewers in August 1991. The main
information collected concerned re-
productive history, waiting time to
pregnancy, and other questions related to
reproduction. Waiting time to preg-

nancy 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 preg-
ancy?” 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
monzygotic, 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 re-
stricted to women who first attempted to become preg-
nant at 20–34 years or 20–29 years of age.

In Table 3, the waiting time to pregnancy distribu-
tion, is given only for the 1953–1966 cohorts to make
the twin and singleton cohorts comparable. Neverthe-
less, 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)

<table>
<thead>
<tr>
<th>Age (Years) at Survey and Zygosity*</th>
<th>Pregnancy Achieved</th>
<th>Still Trying</th>
<th>Gave Up Trying</th>
<th>Pregnant Despite Contraception</th>
<th>Never Tried</th>
<th>Missing Data†</th>
<th>Total (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DZ unlike sexed</td>
<td>4.9</td>
<td>1.0</td>
<td>0.0</td>
<td>3.2</td>
<td>51.1</td>
<td>39.8</td>
<td>963</td>
</tr>
<tr>
<td>DZ like sexed</td>
<td>4.6</td>
<td>0.7</td>
<td>0.4</td>
<td>2.8</td>
<td>51.1</td>
<td>40.5</td>
<td>1,134</td>
</tr>
<tr>
<td>MZ</td>
<td>3.8</td>
<td>1.7</td>
<td>0.2</td>
<td>2.1</td>
<td>53.5</td>
<td>38.8</td>
<td>1,248</td>
</tr>
<tr>
<td>26–29</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DZ unlike sexed</td>
<td>31.8</td>
<td>4.6</td>
<td>0.6</td>
<td>5.7</td>
<td>31.2</td>
<td>26.0</td>
<td>995</td>
</tr>
<tr>
<td>DZ like sexed</td>
<td>31.5</td>
<td>5.2</td>
<td>0.4</td>
<td>5.8</td>
<td>32.1</td>
<td>25.0</td>
<td>1,034</td>
</tr>
<tr>
<td>MZ</td>
<td>32.4</td>
<td>4.2</td>
<td>0.6</td>
<td>4.0</td>
<td>35.9</td>
<td>24.9</td>
<td>935</td>
</tr>
<tr>
<td>30–34</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DZ unlike sexed</td>
<td>59.4</td>
<td>3.8</td>
<td>1.0</td>
<td>7.2</td>
<td>11.6</td>
<td>17.2</td>
<td>1,090</td>
</tr>
<tr>
<td>DZ like sexed</td>
<td>58.6</td>
<td>3.8</td>
<td>0.4</td>
<td>6.8</td>
<td>12.0</td>
<td>18.3</td>
<td>1,168</td>
</tr>
<tr>
<td>MZ</td>
<td>58.4</td>
<td>2.4</td>
<td>1.0</td>
<td>6.8</td>
<td>14.7</td>
<td>16.7</td>
<td>819</td>
</tr>
<tr>
<td>≥35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DZ unlike sexed</td>
<td>60.4</td>
<td>1.6</td>
<td>1.6</td>
<td>8.8</td>
<td>7.3</td>
<td>20.3</td>
<td>1,221</td>
</tr>
<tr>
<td>DZ like sexed</td>
<td>61.8</td>
<td>2.1</td>
<td>1.9</td>
<td>8.5</td>
<td>8.8</td>
<td>17.0</td>
<td>1,119</td>
</tr>
<tr>
<td>MZ</td>
<td>63.9</td>
<td>2.0</td>
<td>1.1</td>
<td>8.2</td>
<td>7.7</td>
<td>17.1</td>
<td>648</td>
</tr>
<tr>
<td>Total (N)</td>
<td>4,744</td>
<td>340</td>
<td>93</td>
<td>713</td>
<td>3,321</td>
<td>3,163</td>
<td>12,374</td>
</tr>
</tbody>
</table>

* DZ = dizygotic; MZ = monzygotic.
† 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 Singleton "Birth Cohort: 1953-1966"

<table>
<thead>
<tr>
<th>% at Age (Years)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>13.3</td>
</tr>
<tr>
<td>21-25</td>
<td>37.3</td>
</tr>
<tr>
<td>26-30</td>
<td>41.2</td>
</tr>
<tr>
<td>31+</td>
<td>8.2</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
</tr>
</tbody>
</table>

A. Pregnant despite contraception excluded
- All twins: 34.6%
- DZ unlike sexed: 24.6%
- DZ like sexed: 24.6%
- MZ: 24.6%
- Singleton: 24.6%

B. Pregnant despite contraception included
- All twins: 34.6%
- DZ unlike sexed: 24.6%
- DZ like sexed: 24.6%
- MZ: 24.6%
- Singleton: 24.6%

- 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.

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. Furthermore, various instruments (interviews and questionnaires) used to assess waiting time to pregnancy have been shown to correlate with differences in population sperm counts.

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. 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. 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. 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. 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. 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, 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

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References