established in the literature: people can suffer a social death before their physical death as society turns away from the dying.[22] Some people's desire to participate in research at the end of life may itself be an example of resistance to social death, an opportunity to be an active and participating citizen again rather than an invalid or patient.

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Sex ratio and time to pregnancy: analysis of four large European population surveys

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ABSTRACT

Objective To test whether the secondary sex ratio (proportion of male births) is associated with time to pregnancy, a marker of fertility.

Design Analysis of four large population surveys.

Setting Denmark and the United Kingdom.

Participants 49 506 pregnancies.

Main outcome measure Secondary sex ratio.

Results No association was found between the sex ratio and time to pregnancy and no discernible trend was found for sex ratio with time to pregnancy, either within individual datasets or in the pooled analysis. The odds ratios were 0.97 (95% confidence interval 0.90 to 1.04) for contraceptive failures, 1.01 (0.96 to 1.05) for time to pregnancy of 2-4 months, 1.02 (0.97 to 1.08) for 5-10 months, 0.98 (0.93 to 1.03) for 11 months or more, and 0.88 (0.74 to 1.06) for fertility treatment, with 0-1 months as the reference category.

Conclusion No association was found between the secondary sex ratio and time to pregnancy.

INTRODUCTION

Evidence exists of a decline in semen quality over recent decades and a deterioration in the reproductive health of males, with an increase in the incidence of testicular cancer and probably of hypospadias and cryptorchidism—the "testicular dysgenesis syndrome." One possible cause is endocrine disruption due to environmental agents with oestrogenic or antiandrogenic effects, although direct evidence is lacking and other mechanisms are possible.[1] Other things being equal, a decline in semen quality is expected to be followed by a declining trend in fertility, although during the same period no such decline—as measured by the time to pregnancy—has been observed.[2]

In parallel, during the same period the proportion of male offspring (the secondary sex ratio) has been declining in many countries, including the United States and Canada and in several European countries.[3 4]

Exposure to certain substances, such as the nematocide dibromochlorpropane,[5] has been found to affect both the secondary sex ratio and male fertility. This parallelism of trend together with shared chemical determinants raises the question of whether the probability of conceiving a male child is linked to the parents' fertility. We tested the hypothesis that the secondary sex ratio

is associated with the time to pregnancy, a marker of fertility, using four datasets from previous population surveys.[6]

METHODS

We used high quality datasets from four European studies with population based samples: the Office for National Statistics omnibus study, the Odense prenatal study, the Asclepios project, and the Millennium cohort study.[2 7-9]

We identified 49 506 liveborn singletons conceived without fertility treatment. Information on conception was obtained by questionnaire. We classified pregnancies into contraceptive failures and those with a time to pregnancy of 0-1 months (reference category), 2-4 months, 5-10 months, and 11 months or more. Data on a further 496 babies born after fertility treatment were available and we included these as an additional category in the pooled analysis across all datasets (numbers were too small for inclusion of this category in the study specific analyses). Data on contraceptive failures were not reliably available from the Millennium cohort questionnaire.

We used logistic regression to examine the association between pregnancy categories and secondary sex ratio, adjusting for birth order, age of both parents (grouped), and study. To account for the lack of independence of observations due to about 40% of couples in the Odense dataset having more than one child, we included a random effect for each couple in the model.

RESULTS

Details of the studies and the distribution of pregnancy categories for each are on bmj.com. No association between secondary sex ratio and degree of fertility was observed for any of the studies separately or when pooled (table). For the pooled analysis the odds ratios were 0.97 (95% confidence interval 0.90 to 1.04) for contraceptive failures and 1.01 (0.96 to 1.05) for time to pregnancy of 2-4 months, 1.02 (0.97 to 1.08) for 5-10 months, and 0.98 (0.93 to 1.03) for 11 months or more, with 0-1 months as the reference category. The odds of having a male offspring after successful fertility treatment were reduced (0.88, 0.74 to 1.06). Although the odds ratios show small departures from 1.0, the confidence intervals all include 1.0 and no trends can be seen for the individual studies or for the pooled analysis. The influence of clustering within couples was negligible, with almost identical results being produced for the analyses including random effects (table) as for those excluding random effects (results not shown).

An analysis using a dichotomous split of time to pregnancy corresponding to "clinical infertility" produced an odds ratio of 0.97 (95% confidence interval 0.93 to 1.03) for those with a time to pregnancy of 12 months or more compared with those classified as contraceptive failures or with a time to pregnancy of less than 12 months.

DISCUSSION

Using datasets from four large European studies we found no association between time to pregnancy (a marker of fertility) and secondary sex ratio (proportion of male births).

A power calculation showed that there was 99%, 93%, and 57% power to detect, respectively, a 4%, 3%, and 2% difference in the percentage of male births between the top and bottom categories, assuming no misclassification of time to pregnancy. Although differences of 2-4% in the secondary sex ratio represent large effects, these were none the less smaller than the 6.5% difference in proportion of male births found by one study,[10] which compared couples with times to pregnancy of less than 12 months with those waiting at least 12 months. Even allowing for non-differential misclassification of time to pregnancy[11] our study was of sufficient power to detect a difference in the proportion of male births similar to that found previously.[10]

Although biases may occur in studies of times to pregnancy,[6] these primarily affect the design, analysis, and interpretation of studies using time to pregnancy as the outcome rather than as a predictor, as in our study. Furthermore, these biases are unlikely to be affected by the sex of the baby. We therefore believe that this is a truly negative study.

Few studies have been published on the possible association between biological fertility and the probability of a male birth. One study found that in a population exposed to pesticides males tended to be conceived more quickly than females.[12] Another study found a deficit of males among pregnancies that took more than a year to achieve.[13] On the other hand, Smits et al found an increasing proportion of males born with longer waiting times to pregnancy.[10] These contradictory findings are based on relatively small studies; there could also be other negative studies that have not been published. Two large unpublished analyses have been

Male births in relation to contraceptive failures and time to pregnancy. Values are odds ratios (95% confidence intervals) unless stated otherwise

Study	No of births	Contraceptive failures	Time to pregnancy (months)*				No of births after fertility treatment
			0-1 (reference group)	2-4	5-10	≥11	
Odense prenatal study	36 674	0.98 (0.91 to 1.06)	1.0	1.00 (0.95 to 1.06)	1.00 (0.94 to 1.07)	0.97 (0.91 to 1.04)	NA
Asclepios project	1797	0.75 (0.52 to 1.08)	1.0	0.93 (0.74 to 1.16)	1.12 (0.82 to 1.52)	1.03 (0.73 to 1.45)	45
Office for National Statistics omnibus study	1817	0.92 (0.69 to 1.24)	1.0	0.99 (0.77 to 1.27)	1.18 (0.85 to 1.63)	1.10 (0.82 to 1.48)	60
Millennium cohort study	9218	NA	1.0	1.05 (0.95 to 1.16)	1.08 (0.95 to 1.22)	0.97 (0.86 to 1.11)	391
Pooled	49 506	0.97 (0.90 to 1.04)	1.0	1.01 (0.96 to 1.05)	1.02 (0.97 to 1.08)	0.98 (0.93 to 1.03)	0.88 (0.74 to 1.06)†

Analyses are adjusted for birth order and parents' age groups, and allow for multiple pregnancies per couple. Pooled analysis is also adjusted for study. NA=not available.
*Values greater than 1.0 indicate increased probability of male births compared with reference group.
†Odds ratio (95% confidence interval) for 496 babies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Semen quality and the probability of a male birth have both declined in recent decades
The two may be linked, as certain chemical agents affect both of them

WHAT THIS STUDY ADDS

No association was found between time to pregnancy and the secondary sex ratio (proportion of male offspring)

posted on the *BMJ* website,[14 15] both of which found no association. Together with our study the sample size is almost 130 000. Although time to pregnancy is affected only by severely abnormal semen quality, this measure should have been sufficient to detect an association, even if it was smaller than that found by Smits et al.[10] Nevertheless, the associations seen in the published studies could have resulted if the populations had been exposed to an environmental agent affecting both the secondary sex ratio and time to pregnancy.[10 12 13]

We were motivated to test our hypothesis because of parallel historical trends in the secondary sex ratio and health of the male reproductive system, as manifest by the testicular dysgenesis syndrome, which could indicate that whatever exposure is responsible for an increasing trend in this syndrome also causes a reduction in the secondary sex ratio. Paternal occupational exposure to the nematocide dibromochlorpropane has been found to greatly impair male fertility; the probability of a male birth was greatly reduced among those men who retained or recovered their fertility.[5] There is also evidence, albeit conflicting, for a similar but weaker effect of exposure to dioxin or dioxin-like polychlorinated biphenyls.[1 16-18]

Our study population covered several European countries, and the observed lack of association between time to pregnancy and the secondary sex ratio suggests that there is no relevant exposure common to all these countries. On the other hand, the population in Smits et al's study was drawn from a region in the Netherlands, which could be exposed to an environmental agent that has not so far been recognised. If so, it would be a valuable clue in an area of research where such clues are urgently needed.

In addition, hypotheses have been put forward that the secondary sex ratio and fertility could be linked through the female reproductive system. Intercourse close to ovulation has been suggested to result in more males.[19] As this would also lead to a relatively high probability of conception, male births would be associated with a shorter time before conception. Others, however, have suggested the opposite.[20] We could find no evidence to support either of these hypotheses.

CONCLUSION

Our findings of no evidence of an association between the secondary sex ratio and time to pregnancy concur with those of other large studies reported on the *BMJ* website.[14 15] The pregnancies that we studied occurred during the past few decades in western Europe, where semen quality is thought to have declined[1] in parallel with a decrease in proportion of male births.[3 4] If these two phenomena were due to the same environmental agent, for example dioxin or another endocrine disruptor, we would expect to have found an association between relatively long times to pregnancy and a decrease in the secondary sex ratio. The lack of an association between the two in our study provides no evidence either of a shared environmental cause or for alternative hypotheses based on female reproductive physiology.

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