FERTILITY AND STERILITY®
VOL. 79, NO. 5, MAY 2003

Published by Elsevier Inc.
Printed on acid-free paper in U.S.A.

Cigarette smoking and the male–female sex ratio

Many industrialized nations have reported a significant drop in the male–female sex ratio at birth, although not all (1–7). While this could be due to an increase in the number of female conceptuses surviving, several studies suggest that fewer males are conceived (8) or survive (9, 10) during maternal stress. Fukuda and coworkers (11) found that both maternal and paternal smoking decreased the sex ratio; they suggested that the stress produced by cigarette smoking may be responsible for the decreased sex ratio.

Their findings bear re-examination for several reasons. The sex ratio in the comparison group of nonsmokers was unusually high, and little information was provided on how subjects were selected for the study. The current study was designed to examine changes in the sex ratio in relation to changes in maternal smoking in a large, unbiased sample—all births in Sweden—and the relationship between maternal smoking around the time of conception and sex ratio in a randomly chosen subgroup of Swedish women for whom detailed smoking histories were available.

Data are collected on all births in Sweden as part of the nationwide Swedish Medical Birth Registry (12). For this study, data from 1983 to 1997 were used to examine trends in maternal smoking and infant sex ratio in live births. At the time of enrollment for prenatal care, usually between 8 and 12 gestational weeks after the last menstrual period, women spend about 1 hour being interviewed and examined by a midwife. Smoking information is collected in a standardized manner using check boxes. Women are categorized as nonsmokers, moderate smokers (1–9 cigarettes per day), or heavy smokers (>10 cigarettes per day). The sex of infants is reported on the pediatric record at delivery. The prenatal care record, labor and delivery record, and pediatric record are all forwarded to the National Board of Health and Welfare, where the information is computerized.

In addition to this general information about maternal smoking collected on the entire Swedish pregnant population, more detailed smoking information was available on a random sample of women selected for a study of tobacco and birth weight. Information on smoking in the 3 months before pregnancy has been collected from women at the time of enrollment for prenatal care since 1999. In all, 26,135 women who delivered singleton live infants in 1999–2000 were selected: 13,092 women who reported smoking at registration for prenatal care and 13,043 women who denied smoking at registration for prenatal care. We wanted to study only those who smoked or did not smoke throughout the periconceptional period. Of the 13,043 women who said that they did not smoke at registration, 9,388 (72%) had information on tobacco use in the 3 months before conception; 8,228 (88%) denied tobacco use both before and after conception. Of the 13,092 women who reported that they were smokers at registration, 9,510 (73%) had information on tobacco use in the 3 months before conception; 9,365 (98%) reported tobacco use during this period. In all 8,542 women were excluded from the analysis: 7,237 because their smoking status in the 3 months before conception was unknown, and 1,305 because they either resumed or quit smoking in the interval between the 3 months before conception and enrollment into prenatal care.

Birth sex ratios were compared by χ^2 tests. Smoking and sex ratio changes over time were examined by the Cochran Mantel-Haenszel correlation test. For the analysis of sex ratio and periconceptional smoking, logistic regression analysis was performed to estimate the odds ratio (OR) for a male infant with respect to smoking status using a 95% confidence interval (CI).

This study received institutional review board exemption because anonymous data were used.

Received June 24, 2002; revised and accepted September 24, 2002.

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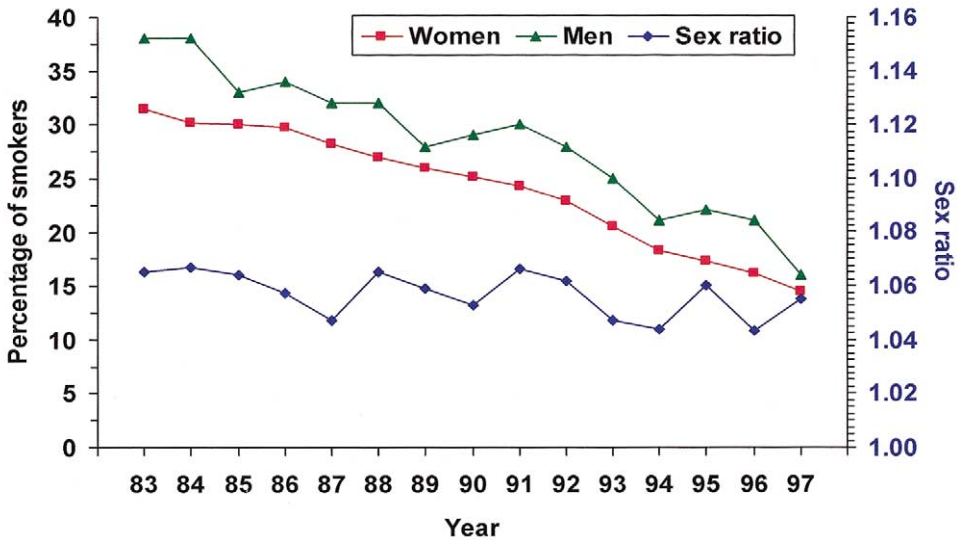
0015-0282/03/$30.00
doi:10.1016/S0015-0282(03)00156-0

Over the 15-year study period, there were 1,552,790 live, singleton births. Gender on each was available on 1,552,539 (99.9%) of those births. The number of births per year ranged from 85,859 to 120,084. The rate of missing data on smoking was 6.1% overall, ranging from 4.1% in 1997 to 8.9% in 1990. Among women who provided information on smoking at entry into prenatal care, the percentage who reported that they smoked fell from 31.3% in 1983 to 14.5% in 1997 (trend test $P<.0001$). Over the same period, the sex ratio fell from 1.064 to 1.055 (trend test $P=.007$; Fig. 1). Thus, the sex ratio actually decreased despite a decrease in the proportion of women exposing their conceptuses to tobacco.

Next, sex ratio was examined by smoking status, first in the subgroup of women who provided data on smoking in the periconceptional period. The sex ratio in the group who smoked (1.06) was not different ($P=.84$) from the sex ratio in the group that did not smoke (1.07). Similarly, when smokers were stratified based on number of cigarettes consumed per day, there was no trend ($P=.88$) toward a lower sex ratio with increasing consumption of cigarettes. Using nonsmokers as the comparison group, the OR for a male infant

FIGURE 1

Trends in smoking by men aged 25–44 years and pregnant women in Sweden with male–female sex ratio, 1983–1997.



Mills. Smoking and sex ratio at birth. Fertil Steril 2003.

was 0.97 (95% CI: 0.89–1.05) among women smoking 1–9 cigarettes per day and was 1.01 (95% CI: 0.95–1.08) for women smoking ≥10 cigarettes per day.

Next, we examined sex ratio by smoking status in the entire cohort entering between 1983 and 1997. The OR for having a male infant by maternal smoking at registration (compared with nonsmokers) was almost identical in both light and heavy smokers. For women smoking 1 to 9 cigarettes per day, the OR was 0.99 (95% CI: 0.98–1.00), and for women smoking ≥10 cigarettes per day, the OR was 0.99 (95% CI: 0.98–1.01). Thus, smoking had no effect on sex ratio in either the cohort for which information on preconception smoking was available or in the larger cohort with information on smoking at registration.

This large, geographically based study showed no association between maternal smoking and lower male–female sex ratio. Moreover, the sex ratio declined significantly over the 15-year study period, despite a highly significant decrease in smoking among pregnant women. As in the large cohort, smoking did not affect the sex ratio in the subgroup of >17,000 women for whom information on smoking before conception was available. Moreover, data on male smoking behavior from Statistics Sweden show that the smoking rate among men likely to become fathers, those aged 25 to 44 years, also declined markedly from 38% in 1983 to 16% in 1997 (Fig. 1). The net effect of this drop in male smoking rates is almost certainly a reduction in maternal exposure to secondhand smoke and a reduction in paternal exposure to toxins in cigarettes.

These results speak very strongly against a maternally or environmentally mediated effect of smoking on sex ratio. Indeed, the lower confidence limits of our calculated ORs of the sex ratio for smokers vs. nonsmokers in both the large cohort (0.98) and the cohort with more detailed smoking histories (0.89 and 0.95 for light and heavy smokers, respectively) exclude the ORs reported for maternal smoking in the previous study. Fukuda et al. (11) reported ORs ranging from 0.87 to 0.78 for women smokers depending on the smoking status of the fathers. It should be noted that our data cannot exclude an effect of paternal smoking on sperm rather than on the conceptus after conception, but a sperm effect could not account for the finding in the previous study that women smokers had decreased sex ratios as well as men.

Our study differs in several ways from the Japanese study. Ours was very large and geographically based, including the entire country of Sweden. Thus, selection of subjects for study could not be a problem in our investigation. The sex ratio in the Japanese sample of nonsmokers was noted by the authors to be much higher than the ratio for the geographic area in general and could have inflated the effect seen in smokers. The Japanese study had information on paternal smoking; as noted above, we cannot exclude the possibility that tobacco could selectively kill or damage sperm bearing the Y chromosome, although we know of no data to support this theory.

Our study was able to examine trends in sex ratio and smoking over a 15-year period, demonstrating a fall in sex ratio despite decreasing exposure to tobacco, thus making tobacco an unlikely explanation for the change.

In summary, our results indicate that maternal smoking or environmental exposure to tobacco smoke are unlikely explanations for the decreased proportion of male live births seen over the last 15 years.

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