Parental Infertility and Semen Quality in Male Offspring: A Follow-up Study

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Jensen et al. (Am J Epidemiol 2007;165:583–90) reported for the first time that men whose mothers had received fertility treatment had poor semen quality. This result could be confounded by the mothers’ body mass index. Obesity is a strong predictor of fecundity and could have a programming effect on semen quality through hormonal factors or links to fetal growth. The authors of the current study tried to replicate the finding of Jensen et al. after controlling for maternal body mass index and other covariates using data from a recently conducted, population-based, Danish follow-up study on the association between maternal smoking during pregnancy in 1984–1987 and sons’ semen quality, in which the participants were sampled according to levels of maternal smoking during pregnancy. After adjustment, sons of mothers who reported that they had been examined or treated for childlessness (n = 30) had a lower sperm concentration and total sperm count and fewer motile and morphologically normal spermatozoa in comparison with sons of mothers who had not been examined or treated for childlessness (n = 295). None of the differences (except for semen concentration) between the groups reached statistical significance, but the study has limited power. The findings were in the same direction as those reported by Jensen et al. and do not indicate that their results are confounded by maternal body mass index.

Jensen et al. (1) reported for the first time that men whose mothers had received fertility treatment had poor semen quality. If infertility treatment causes poor semen quality in the offspring, it is important because more and more women receive this treatment. The results may, however, be confounded by the parents’ infertility (confounding by indication) or by other confounders, such as the mothers’ body mass index. Obesity is a strong predictor of fecundity (2, 3) and may have a programming effect on semen quality, for example, by a higher level of estrogen exposure during fetal life, which may disturb the endocrinologic control of the male fetal urogenital organs (4). Lipophilic persistent organic pollutants, such as polychlorinated biphenyls, accumulate in adipose tissue and are found in the umbilical cord, as well as in pregnant women (5). They have been linked with poor semen quality (6).

We recently conducted a population-based, follow-up study on the association between maternal smoking during pregnancy and semen quality (7). In this cohort, we have data on maternal prepregnant height and weight and can therefore examine if adjustment for body mass index eliminates an association between infertility and semen quality in the offspring.

MATERIALS AND METHODS

The participants in our study were sons of mothers who, during their pregnancies from 1984 to 1987, participated in the “Healthy Habits for Two” cohort (8). The mothers provided information on lifestyle factors during pregnancy and whether they had been examined or treated for childlessness.
The information was collected by self-administered questionnaires handed out by the midwives around the 36th week of gestation. Their sons, who were alive and living in Denmark by December 2004, were identified in the Danish Civil Registration System (n = 5,109), and letters of invitation were sent to 716 of these. Since we analyzed data from a study designed to examine the association between prenatal smoking exposure and adult semen quality, the participants were selected according to levels of maternal smoking during pregnancy. A total of 347 (49 percent) men gave consent and participated in the original study. There was no difference in the proportion of men with diseases of the reproductive organs (including cryptorchidism and hypospadias) between participants and nonparticipants.

Information on whether the mother had been examined or treated for childlessness was available for 344 men, and information on maternal prepregnant body mass index was available for 328 men, leaving 325 (94 percent) men available for analysis. (Refer to reference 7 for detailed information on selection and enrollment procedures.)

Each man provided a semen sample, with analysts blinded to information on infertility treatment and any other information obtained during pregnancy. The semen samples were analyzed in accordance with the information obtained during pregnancy. The semen samples were blinded to information on infertility treatment and any other information on selection and enrollment procedures.

TABLE 1. Semen characteristics among 325 men living in Denmark in 2004 stratified by maternal examination or treatment for childlessness

<table>
<thead>
<tr>
<th>Mother examined or treated for childlessness</th>
<th>Yes (n = 30)</th>
<th>No (n = 295)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted back-transformed mean†</td>
<td>95% confidence interval</td>
<td>Adjusted back-transformed mean†</td>
</tr>
<tr>
<td>Sperm concentration (millions/ml)</td>
<td>33.1</td>
<td>19.6, 51.7</td>
<td>55.6</td>
</tr>
<tr>
<td>Semen volume (ml)</td>
<td>4.0</td>
<td>3.3, 4.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Sperm total count (millions)</td>
<td>141</td>
<td>78, 231</td>
<td>189</td>
</tr>
<tr>
<td>Normal-morphology sperm (%)</td>
<td>3.9</td>
<td>2.5, 5.7</td>
<td>5.1</td>
</tr>
<tr>
<td>Motile sperm (%)</td>
<td>65</td>
<td>55, 73</td>
<td>69</td>
</tr>
</tbody>
</table>

* Differences between means were tested by multiple regressions.
† Back-transformed means were adjusted for abstinence time (<2 days, ≥2 days), history of diseases of the reproductive organs (varicocele, hydrocele, orchitis, or chlamydia—yes or no), maternal smoking during pregnancy (yes or no), and maternal prepregnant body mass index (<18.50 kg/m², 18.50–24.99 kg/m², ≥25.00 kg/m²).

Abstinence time of 2 days or more, no diseases of the reproductive organs, no maternal smoking during pregnancy, and maternal prepregnant body mass index of 18.50–24.99 kg/m² are the reference categories.

RESULTS

The 325 participants were from 18 to 21 (median: 20) years of age.

When we compared sons of mothers who reported that they had been examined or treated for childlessness (n = 30) with sons of mothers who reported that they had not been examined or treated for childlessness (n = 295), “exposed” men had a lower sperm concentration and total sperm count and fewer motile and morphologically normal spermatozoa (table 1). The differences between the groups were statistically significant only for sperm concentration. We repeated the analysis after additional adjustment for cryptorchidism and hypospadias and found results similar to those reported in table 1.

Stratification on maternal prepregnant body mass index showed tendencies toward lower sperm concentration and percentage of motile sperm among the exposed men in comparison with the “unexposed” men in all three body mass index levels (<18.50 kg/m², 18.50–24.99 kg/m², ≥25.00 kg/m²), but the association appeared to be strongest for sons of...
mothers who had a body mass index of 25.00 kg/m² or
greater (numbers too small for statistical analysis).

DISCUSSION

Our data do not indicate that the results found by Jensen
et al. were confounded by maternal body mass index. It is
unknown whether the poor semen quality is related to in-
fertility treatment or is caused by male or female infertility
itself, for instance, through hereditary factors. It is important
to get data that can address this issue, since it is plausible
that some infertility treatments may impact organogenesis
and function of the testis.

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