Original Contribution

Maternal Smoking, Alcohol Consumption, and Caffeine Consumption during Pregnancy in Relation to a Son’s Risk of Persistent Cryptorchidism: A Prospective Study in the Child Health and Development Studies Cohort, 1959–1967

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The Child Health and Development Studies is a ≥40-year follow-up of 20,754 pregnancies occurring between 1959 and 1967 in California. There were 84 cases of undescended testes at birth persisting to at least age 2 years among 7,574 liveborn sons whose mothers were interviewed in early pregnancy. Cases were matched to three controls on birth year and race. Compared with mothers of controls, mothers of cryptorchid boys consumed more caffeine during pregnancy (odds ratio = 1.4, 95% confidence interval: 1.1, 1.9 for an interquartile range equivalent to three cups of coffee per day) but were not more likely to smoke or drink alcohol when all behaviors were considered together. Other maternal and perinatal risk factors were not significantly associated with persistent cryptorchidism and did not confound the association with caffeine.

alcohol drinking; caffeine; cryptorchidism; pregnancy; prospective studies; risk factors; smoking

Abbreviation: CHDS, Child Health and Development Studies.

The prevalence of cryptorchidism is highly dependent on case definition and ranges from 0.5 percent if defined as undescended testis at 1 year of age or older to as high as 6.9 percent in newborn boys (1–3). Undescended testicles in newborn boys usually spontaneously descend within the first 6 months of life and can be predominantly linked to prematurity (2, 4–6). The risk factors for persistent cryptorchidism may be different, however.

Of the 12 studies known to investigate maternal smoking and cryptorchidism (1, 7–17), four reported a significantly positive association. Alcohol and coffee consumption in pregnancy are also associated with adverse pregnancy outcomes (18–20), and these behaviors often also covary with smoking (21, 22). Fewer studies report on maternal alcohol (1, 12–15, 23, 24) and caffeine (13) consumption in relation to cryptorchidism, nor do most studies adjust smoking associations for alcohol and caffeine.

In the present study, we investigated associations of maternal smoking, alcohol consumption, and caffeine consumption with persistent cryptorchidism in a large prospective pregnancy cohort, the Child Health and Development Studies (CHDS).

MATERIALS AND METHODS

Study population and design

Subjects in this study were the sons of women who participated in the CHDS (25). The CHDS consists of a ≥40-year follow-up of about 15,000 families, representing 20,754 pregnancies, and 7,574 liveborn male offspring whose mothers were interviewed early in pregnancy. Members of the Kaiser Permanente Health Plan residing in the San Francisco East Bay Area of California and pregnant...
between 1959 and 1967 were eligible for the study. Nearly all eligible pregnancies were included. Follow-up of CHDS births for anomalies in the first 5 years of life was nearly 100 percent complete, making this follow-up for birth defects one of the longest and most comprehensive in the United States. The CHDS is among the largest pregnancy cohorts in the United States, with follow-up for cancer incidence and mortality over more than 40 years. The institutional review board of the Public Health Institute (Oakland, California) approved the protocols for this study.

Cryptorchidism was defined as one or two undescended testicles present at both birth and 2 years of age. We required presence of the condition at age 2 years specifically to examine risk factors for persistent cryptorchidism. Cases for whom a maternal interview was lacking or who were of unknown race/ethnicity were excluded from analysis. For each of the 84 remaining cases, three noncases (controls) were identified who matched the case on race/ethnicity and date of birth. Controls were selected at random from the pool of matches if more than three were available.

### Variables

The primary risk factors examined were maternal cigarette smoking, alcohol consumption, and caffeine consumption during pregnancy. These factors were assessed by a structured interview conducted during early pregnancy.

Number of cigarettes smoked per day was recorded as follows: 0, 1–4, 5–9, 10–14, 15–19, 20–29, 30–39, 40–60, and over 60. Additionally, the original variable was recoded as a dichotomized variable for those smoking 20 or more cigarettes per day versus those smoking fewer than 20 cigarettes per day.

In the structured interview, the mother’s alcohol consumption was ascertained by asking how many glasses of beer, wine, or whiskey she drank in a week. Total drinks of alcohol consumed per week was obtained by adding the number of glasses drunk per week for the three beverages. For each beverage, the number of glasses per week was coded as follows: none or less than one glass per month = 0; less than one glass per week = 0.3; one to eight glasses per week = 1, 2, 3, 4, 5, 6, 7, or 8; and nine or more glasses per week = 9.

#### TABLE 1. Distribution of maternal risk factors for cryptorchidism among cases and controls in the Child Health and Development Studies, California, 1959–1967

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.*</td>
<td>%</td>
</tr>
<tr>
<td>Cigarette smoking (cigarettes/day)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstainers</td>
<td>43</td>
<td>51.2</td>
</tr>
<tr>
<td>Users</td>
<td>41</td>
<td>48.8</td>
</tr>
<tr>
<td>Alcohol consumption (drinks/week)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstainers</td>
<td>28</td>
<td>41.2</td>
</tr>
<tr>
<td>Consumers</td>
<td>40</td>
<td>58.8</td>
</tr>
<tr>
<td>Caffeine consumption (equivalent cups of coffee/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstainers</td>
<td>6</td>
<td>8.6</td>
</tr>
<tr>
<td>Consumers</td>
<td>64</td>
<td>91.4</td>
</tr>
<tr>
<td>Parity (no. of prior births)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>29</td>
<td>34.5</td>
</tr>
<tr>
<td>One or more</td>
<td>55</td>
<td>65.5</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>55</td>
<td>65.5</td>
</tr>
<tr>
<td>African American</td>
<td>22</td>
<td>26.2</td>
</tr>
<tr>
<td>Asian</td>
<td>5</td>
<td>6.0</td>
</tr>
<tr>
<td>Mother’s age (years)</td>
<td>84</td>
<td>28.0</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>80</td>
<td>22.1</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>84</td>
<td>3.3</td>
</tr>
<tr>
<td>Length of gestation (days)</td>
<td>84</td>
<td>279.0</td>
</tr>
</tbody>
</table>

* Numbers of cases and controls differ because of missing data on some characteristics.
† Calculated by subtracting the 25th percentile from the 75th percentile.
‡ Controls: 0 cigarettes/day = 42.7%, 1–9/day = 26.1%, 10–19/day = 12.5%, ≥20/day = 18.6%; cases: 0 cigarettes/day = 51.2%, 1–9/day = 25%, 10–19/day = 8.3%, ≥20/day = 15.5%.
Caffeine intake was derived by assuming that an 8-ounce serving of coffee contained 135 mg of caffeine and an 8-ounce serving of tea contained 43.75 mg of caffeine (26). The interview asked how many cups of coffee and tea were drunk per day, and this information was coded as for the alcohol consumption question. To obtain total caffeine intake in milligrams per day, the reported number of cups of coffee drunk per day multiplied by 135 was added to the reported number of cups of tea drunk per day multiplied by 43.75. This figure was rescaled by dividing it by 135, making one unit on the new scale the equivalent of one serving of coffee.

Other variables were examined as potential confounders, including mother’s age, mother’s weight, mother’s height, mother’s body mass index (weight (kg)/height (m)²), number of previous livebirths, pregnancy complications, infant’s birth weight, infant’s birth length, and length of gestation. These data were abstracted from medical records and are not subject to recall bias.

**Statistical methods**

Associations between case status and the primary risk factors were examined by using conditional logistic regression analysis. Where possible, models contained continuous variables and the interquartile range was used to determine an odds ratio. Models provided maximum likelihood estimates of odds ratios and approximate 95 percent confidence intervals (27).

Unadjusted, bivariate, and multivariate models were examined with maternal alcohol consumption, smoking, caffeine consumption, body mass index, and son’s birth weight, because these characteristics are known to be correlated and are suspected to be risk factors for cryptorchidism. All models were run by using only cases with nonmissing information for all variables (68 cases and 212 controls). All analyses were performed by using version 8.2 of SAS software (SAS Institute, Inc., Cary, North Carolina).

**RESULTS**

CHDS mothers reported higher levels of smoking, alcohol consumption, and caffeine consumption than mothers in most studies conducted well after public health warnings against these behaviors during pregnancy had become common knowledge. (This information is described in three supplemental tables, which are posted on the journal’s website [http://aje.oupjournals.org/].)

The race/ethnicity distribution among cryptorchidism cases was similar to that for the overall CHDS cohort: 65.5 percent Caucasian, 26.2 percent African American, and 6.0 percent Asian. Distributions of analysis variables for cases and controls, without accounting for matching, are shown in table 1.

A significant association was found for caffeine consumption, both before and after adjustment for alcohol consumption, smoking, birth weight, and body mass index (table 2). Different formulation of the smoking variable did not change the association. There was no evidence that other perinatal characteristics were confounders or mediators of the caffeine association with cryptorchidism, nor were these characteristics significant predictors of persistent cryptorchidism in this cohort. Most of the perinatal characteristics examined were rare among cases and controls (table 1).

**DISCUSSION**

**Smoking**

The present study affords some advantages for assessing maternal exposures to smoking. Exposure data were collected prospectively between 1959 and 1967, prior to the 1980 Surgeon General’s Report on the Health Consequences of Smoking for Women (18). The prospective study design eliminates recall bias, and collecting data about behavior before it was stigmatized might also reduce other forms of information bias. A prior report based on the CHDS showed a consistent correlation between serum cotinine and self-reported smoking (28), lending further validity to the assessment of smoking exposure in the present study.

Despite a higher smoking prevalence in our cohort compared with most other previous studies, we found...
a nonsignificant decrease in risk of cryptorchidism associated with maternal smoking. Although this finding contradicts prior literature, which reported either a significantly positive association (1, 7, 12, 17) or no association (8–11, 13–16), there are many differences between our study and previous research. Most prior studies were retrospective case-control studies with less precise case definitions for cryptorchidism and were limited to binary exposure data. It is likely that our study had the advantage of lower reporting bias simply because of the lack of stigmatization of smoking and drinking behaviors. In addition, we were able to adjust smoking effects for alcohol and caffeine consumption. The most comparable prior study also found no association between smoking and cryptorchidism (16); however, another prospective study did find an effect (17). We suggest that the most likely explanation for the difference in results between the studies is differences in case definition. It is possible that smoking is more strongly associated with cryptorchidism that spontaneously resolves in the first 2 years of life. Our study was smaller, and lower power could therefore explain why we found no association between maternal smoking and cryptorchidism.

Alcohol consumption

We observed no significant association between maternal alcohol consumption and cryptorchidism, despite higher consumption levels than in most previous studies. Two prior studies found an association between maternal alcohol consumption and cryptorchidism, but one did not evaluate persistent cryptorchidism (23) and the other was retrospective and did not adjust for correlated behaviors such as smoking and coffee intake (24). Reporting bias may be a significant concern for retrospective case-control studies conducted after the discovery of fetal alcohol syndrome in the 1970s because mothers of cases may be motivated to either underreport or even overreport alcohol consumption.

Caffeine consumption

Coffee consumption in pregnancy has been linked to pregnancy complications such as intrauterine growth retardation (29, 30) and spontaneous abortion (30–32). We observed a significantly increased risk of cryptorchidism for sons of mothers who consumed more caffeine during pregnancy. In the only prior study of caffeine consumption and cryptorchidism that we could identify, Berkowitz and Lapinski (13) found a nonsignificant increased risk from caffeinated coffee. Caffeine intake in our study population was much higher and was mostly representative of coffee drinkers because few women drank tea. It may be that our observation of a significant risk associated with caffeine consumption is due to the wide range of caffeine consumption in our study and the ability to study caffeine consumption as a continuous variable.

We were unable to assess caffeine exposure due to soft drink consumption. Because soda consumption has increased dramatically since the late 1970s (33–35), an investigation of such information during the 1960s might still be relevant. Additionally, we could not separate the effects of other components of coffee from the effects of caffeine.

Other risk factors

We did not observe significant associations between perinatal risk factors and risk of cryptorchidism, which may be the result of the small sample size or our case definition for cryptorchidism. Because premature boys are more likely to be cryptorchid at birth (4, 5) and also more likely to experience spontaneous testicular descent before their first birthday (2), our case definition may have selected for persistent cryptorchidism because of factors other than prematurity.

In accordance with a prior study based on the Collaborative Perinatal Study reported by McGlynn et al. (16), we found that rates of cryptorchidism by race closely matched the racial frequency of the general cohort as a whole.

Summary

We found evidence that maternal caffeine consumption during pregnancy may increase the risk of cryptorchidism. Although the small sample size limited conclusions about negative findings, the timing of exposure assessment and the range of exposures observed provided a unique opportunity to observe a sizable effect for maternal smoking, alcohol consumption, and caffeine consumption. Simultaneous consideration of smoking, alcohol consumption, and caffeine consumption in pregnancy is probably essential in further studies; however, the stigmatization of these behaviors in pregnancy presents challenges for exposure ascertainment.

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The point of view and conclusions expressed in this paper are those of the authors and do not necessarily represent the official position or policies of the Lance Armstrong Foundation. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government.

Conflict of interest: none declared.

REFERENCES


