ABSTRACT. **Objective.** To determine the association between light-to-moderate prenatal alcohol exposure and congenital renal anomalies.

**Methods.** Data from the population-based Atlanta Birth Defects Case-Control Study were used to examine the association between selected renal anomalies and self-reported maternal alcohol consumption during the period from 1 month before through 3 months after conception. Case infants were ascertained by a population-based birth defects registry with active case ascertainment; the case group consisted of 158 infants, born during 1968 through 1980 to metropolitan Atlanta residents, in whom these renal anomalies had been diagnosed. Two control groups were used. One had 3029 infants without birth defects, and the other had 4633 infants with birth defects exclusive of the urinary tract who were born during the same period.

**Results.** Overall, there was a moderate association between renal anomalies and moderate prenatal alcohol exposure (odds ratio, 1.5; 95% confidence interval, 1.0 to 2.3). When the renal anomalies were subclassified, moderate prenatal alcohol exposure was significantly associated only with renal agenesis or hypoplasia (odds ratio, 2.5; 95% confidence interval, 1.2 to 5.1), and within this group only infants with bilateral defects and other major anomalies in addition to renal agenesis or hypoplasia had significantly elevated risks. There were no significant associations between reported light consumption and any category of the selected renal anomalies. No conclusions could be reached for reported heavy consumption because of sparse data. Adjustments for potential confounding factors did not alter these results.

**Conclusion.** This study suggests that moderate alcohol consumption during pregnancy may increase a woman’s risk of giving birth to a child with renal agenesis or hypoplasia.

**ABBREVIATIONS.** ABDDCS, Atlanta Birth Defects Case-Control Study; OR, odds ratio.

Investigations of a possible association between women’s light-to-moderate alcohol consumption during pregnancy and congenital anomalies among their children have produced mixed results. Multiple adverse reproductive outcomes, including increased minor and/or major congenital anomalies, have been reported from some cohort and cross-sectional studies and clinical case series that have examined the effect of moderate alcohol exposure in utero. Other studies have found no increase in congenital anomalies among infants with moderate in utero exposure to alcohol, but many have reported a significant increase among infants with heavy exposure.

The specific association between in utero alcohol exposure and renal anomalies comes from several case reports and clinical case series in humans, usually infants and children with fetal alcohol syndrome, and from experimental studies in animals. Both the human and animal studies most often examined the effects of heavy exposure. However, Taylor and associates recently studied 84 individuals who had had first trimester exposure of 2 or more absolute oz of alcohol per day and did not find them to have an increased rate of renal anomalies. Finally, a large cohort study reported by Mills and Graubard, which evaluated the effects of moderate alcohol exposure, found a dose-response relationship between in utero alcohol exposure and genital tract anomalies and raised the possibility that there may be some malformations for which any drinking increases the risk. The classification schema for the level of alcohol consumption varied considerably among the studies we reviewed.

In this study, we evaluated the association between light-to-moderate alcohol consumption during pregnancy and the birth prevalence of selected renal anomalies among their offspring using data from a large population-based, case-control study. To our knowledge, this is the first population-based study to explore possible relationships between renal anomalies and prenatal alcohol exposure.

**METHODS**

**Study Population**

We used data originally collected as part of the Atlanta Birth Defects Case-Control Study (ABDDCS), a large, population-based investigation conducted by the Centers for Disease Control and Prevention in 1982 and 1983. The purpose of the study was to identify risk factors for major birth defects; the study was primarily conducted to determine whether men who had served in the US military in Vietnam were at increased risk of fathering children with congenital anomalies.

The case infants were 4918 infants who were initially ascertained by a population-based birth defects surveillance system, the Metropolitan Atlanta Congenital Defects Program. All case in-
fants had serious congenital anomalies diagnosed in the first year of life, were either live born or stillborn at 20 weeks’ gestation or later, were born from 1968 through 1980, and had mothers who were residents of metropolitan Atlanta at the time of delivery. The control group comprised 3029 infants with no reported congenital anomalies. They were randomly chosen from birth certificates of a disease in a population attributed to a particular risk factor) and were adjusted for potential confounders included maternal age (<20, 20–34, and ≥35 years), education, and race; whether mothers smoked, had diabetes mellitus, or used vitamins between 3 months before and the first 3 months after conception; and period of birth. We included vitamin use as a confounder because multivitamin use among pregnant women in their first trimester was recently reported to have a protective effect against congenital urinary tract anomalies among their children.10,26 Because there were no significant differences between the models with and without these potential confounders, we present the results of the crude analyses. We also present the results of crude analyses for some subgroups of defects (eg, renal agenesis and hypoplasia, multiple with renal atresia) that occurred too infrequently for meaningful analysis by logistic regression.

We calculated the attributable fraction (AF, the fraction of cases of a disease in a population attributed to a particular risk factor) using the formula of Miettinen26 \[ AF = \frac{f}{R - 1}/R \], where \( f \) is the fraction of cases with the moderate in utero alcohol exposure, and \( R \) is the OR.24

**RESULTS**

Table 1 shows the association between maternal light-to-moderate alcohol consumption and the occurrence of selected renal anomalies. Infants exposed in utero to 14 or more drinks per week (heavy consumption) were included in this table, but data are sparse.

Of the 2886 mothers of control infants with no anomalies, 847 (29.3%) reported consuming more than zero but fewer than three drinks per week, whereas of the 148 mothers of infants with renal anomalies, only 34 (22.3%) reported drinking that amount, thus showing no significant association between this low level of in utero alcohol exposure and renal anomalies. In addition, we found no significant association between this level of in utero exposure and any of the subgroups of renal anomalies. The OR for multicystic dysplasia was elevated at 2.4; however, four infants with this defect were excluded because of missing variables necessary to calculate the number of drinks that their mothers consumed per week. Other variables indicate that these mothers were probably nondrinkers; thus the OR may be falsely elevated.

Of the 2886 mothers of control infants with no anomalies, 428 (14.8%) reported consuming from 3 to 13 drinks per week. Of the 148 mothers of case infants, 32 (21.6%) reported a similar exposure, which yielded an OR of 1.5, which was not significant. On subgroup analysis, only renal agenesis was significantly associated with moderate in utero exposure (OR, 2.5; 95% confidence interval, 1.2 to 5.1).

**Statistical Methods and Analyses**

We compared case and control infants with respect to maternal alcohol consumption. We calculated odds ratios (ORs) and 95% confidence intervals and used unconditional logistic regression to adjust for potential confounders. Potential confounders included maternal age (<20, 20–34, and ≥35 years), education, and race; whether mothers smoked, had diabetes mellitus, or used vitamins between 3 months before and the first 3 months after conception; and period of birth. We included vitamin use as a confounder because multivitamin use among pregnant women in their first trimester was recently reported to have a protective effect against congenital urinary tract anomalies among their children.10,26

**TABLE 1.** Association Between Selected Renal Anomalies and Mothers’ Light-to-Moderate Alcohol Consumption During Pregnancy: Atlanta Birth Defects Case-Control Study, 1968 Through 1980

<table>
<thead>
<tr>
<th>Type of Renal Anomaly</th>
<th>None, n</th>
<th>OR (95% CI)</th>
<th>3–13</th>
<th>OR (95% CI)</th>
<th>14+</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No anomaly</td>
<td>1576</td>
<td>847</td>
<td>0.8 (0.5–1.2)</td>
<td>32</td>
<td>1.5 (1.0–2.3)</td>
<td>3</td>
</tr>
<tr>
<td>All renal anomalies</td>
<td>79</td>
<td>34</td>
<td>0.5 (0.2–1.4)</td>
<td>14</td>
<td>2.5 (1.2–5.1)</td>
<td>0</td>
</tr>
<tr>
<td>Agenesis/hypoplasia</td>
<td>21</td>
<td>6</td>
<td>1.0 (0.5–2.1)</td>
<td>11</td>
<td>2.0 (1.0–5.2)</td>
<td>2</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>40</td>
<td>10</td>
<td>1.1 (0.3–4.0)</td>
<td>4</td>
<td>2.1 (0.5–8.0)</td>
<td>0</td>
</tr>
<tr>
<td>Duplication</td>
<td>17</td>
<td>4</td>
<td>2.4 (1.0–5.6)</td>
<td>3</td>
<td>1.0 (0.2–3.9)</td>
<td>1</td>
</tr>
<tr>
<td>Multicystic dysplasia</td>
<td>11</td>
<td>14</td>
<td>0.5 (0.2–1.0)</td>
<td>2</td>
<td>1.0 (0.5–2.1)</td>
<td>3</td>
</tr>
</tbody>
</table>

* n indicates number of infants; OR, odds ratio; and CI, confidence interval.
We further subdivided the hydroureter or hydronephrosis group according to the level or type of obstructive lesion (ie, ureteropelvic junction and ureter, ureterovesical junction, bladder neck and posterior urethra, posterior urethral valves, and unspecified). However, no level of in utero alcohol exposure was significantly associated with any of these subgroups, and the results are not presented in this article.

As shown in Table 2, light in utero exposure to alcohol was not significantly associated with renal agenesis and hypoplasia, but moderate exposure was. In this analysis, infants were further subdivided into those with unilateral or bilateral defects and those in whom the defects were isolated or single components of multiple congenital anomalies. No association between light consumption and any subgroup of renal agenesis or hypoplasia was seen. However, among children of mothers with histories of moderate consumption, ORs were elevated for all subgroups of defects but were significantly elevated only in the bilateral and multiple subgroups.

Table 3 shows the association between binge drinking among moderate drinkers and their risk of having children with renal agenesis or hypoplasia. There was a significant association between binge drinking and all renal agenesis or hypoplasia. Although the ORs were elevated for each of the subgroups of this class of anomaly, they were statistically significant only for bilateral defects and multiple congenital anomalies. However, among mothers of both case and control infants, those who were binge drinkers had a higher number of drinks per week than those who did not binge. Therefore, it is difficult to disentangle the effect of quantity of alcohol from the binge pattern.

The association of various combinations of structural anomalies with light-to-moderate maternal alcohol consumption is shown in Table 4. Only major anomalies that were unrelated to the renal anomalies and occurred more than once in the exposed infants are shown. Combinations that are not shown because they occurred only once in the exposed infants included tracheoesophageal fistula, unilateral lung agenesis, omphalocele, unspecified accessory digits, and agenesis of the gallbladder. Only anal atresia and major cardiac defects in conjunction with renal agenesis or hypoplasia showed a significant association with moderate exposure. The types of cardiac defects were varied and included unspecified ventricular septal defects in two infants and coarctation of the aorta, an atrial septal defect, and aortic and mitral valve hypoplasia in only one infant each. Of the two infants with cardiac defects, one also had anal atresia, and another had hemivertebrae. No multiple defect combination was significantly associated with light maternal alcohol consumption.

For all analyses, we used a second control group composed of infants with congenital anomalies exclusive of the urinary tract. The results of the analyses with this second control group were not appreciably different from those with the first group, and they are not included in this report.

The attributable fractions for moderate alcohol exposure and two subgroups of renal agenesis and hypoplasia, bilateral and multiple defects, were 33% and 22%, respectively. If the association between renal agenesis or hypoplasia and moderate maternal alcohol consumption during pregnancy is causal, we estimate that 22% of the multiple anomaly cases and 33% of bilateral defect cases may be attributed to this exposure.

**DISCUSSION**

The main finding of this study was a significant association between a pregnant woman’s reported moderate alcohol consumption and renal agenesis or hypoplasia among her offspring. This association was stronger for infants with bilateral defects and for infants who had multiple congenital anomalies, in particular anal atresia and major cardiac defects. However, given the rarity of renal agenesis or hypoplasia in the general population, the absolute risk for this defect among offspring of women who consume moderate amounts of alcohol during the first trimester is less than 1 in 1000 exposed births. There were no significant associations with other studied renal anomalies and reported moderate consumption and no significant associations between any category of renal anomalies and reported light consumption. Reported heavy consumption was rare in the study population; therefore, no conclusions could be reached for this consumption category because of sparse data.

Before interpreting these results, it is important to consider the strengths and limitations of the study. Because we derived our data from a population-based study with a relatively large number of births,
it was not subject to the selection bias found in most clinic- or hospital-based studies, and there were enough participants in the study to detect small excess risks. The diagnosis data were based on multiple sources of ascertainment, and because the data were collected before there was widespread use of prenatal diagnosis, there was probably little bias introduced by pregnancies being selectively terminated before 20 weeks’ gestation. Additionally, the interview data were collected before there was widespread knowledge of alcohol-related congenital anomalies, knowledge that could perhaps cause a woman to be reluctant to disclose her alcohol consumption during pregnancy.

The study has several limitations. Renal anomalies are variably ascertained and classified; however, 67% of the infants in the renal agenesis or hypoplasia group did have autopsies. In addition, infants with other major congenital anomalies and those who are stillborn or die shortly after birth may be studied more completely than those with isolated and/or unilateral defects. The renal defects studied are most likely heterogeneous in both cause and pathogenesis, and one or more of the case infants may have had an undiagnosed genetic syndrome. There were small numbers of case infants, especially in the subgroups with additional anomalies.

The level of alcohol exposure is difficult to quantify. The structure of the questionnaire does not allow for easy determination of the amount of absolute alcohol ingested per week. There were variable periods between exposure and administration of the questionnaire. In addition, we are relying on self-reported exposure data, which may be subject to recall bias. However, the results of analyses with a control group of infants with congenital anomalies indicate that this was not a significant problem in this study. Comparing the results of this study with those of other studies is complicated by the variation in alcohol consumption classification.

Animal studies give some support to the biological plausibility of the study finding. In mice, Gage and Sulik demonstrated that ethanol caused excessive cell death in the region of the developing mesonephric duct just proximal to the cloaca and in the pre-paragraphal neural crest cell located just proximal to the posterior neuropore. However, the resultant defects in these mice were hydronephrosis and hydroureter, not renal agenesis or hypoplasia. In light of our elevated OR for renal or ureteral duplication, it is interesting that the hydronephrosis was commonly caused by duplicate ureteral lumens. In monkeys, Mukherjee and Hodgen observed that maternal ethanol exposure in the third trimester induced transient impairment of umbilical circulation and resultant fetal hypoxia. Human umbilical blood vessels from full-term pregnancies were subsequently reported to spasm when exposed to ethanol. Whether this effect could be produced earlier in pregnancy and to a sufficient degree to cause hypoperfusion of the developing kidney and other organs is unknown.

Previous studies of the relationship between ma-
ternal alcohol consumption and renal anomalies have produced varying results, as discussed previously. We found that prenatal alcohol exposure was most highly associated with renal agenesis or hypoplasia in conjunction with bilateral defects and/or multiple congenital anomalies. Because infants with these anomalies are more likely to be stillborn or to die shortly after death (74% in this study), studies that ascertain cases after the neonatal period will miss an association between moderate alcohol exposure and these defects.

The literature is also divided on the effect that maternal binge drinking has on a child's risk of congenital anomalies in general. Studies with both positive and negative results are reported.8,12,14 Although among women who drank moderately we found a significant association between binge drinking and their children's risk of renal agenesis or hypoplasia, we cannot interpret this finding with the available data.

Even in view of the limitations of this study, we think that the findings are important and warrant further investigation in studies with better measures of both exposure and outcome. If our results are confirmed by other studies, moderate alcohol consumption during pregnancy could be identified as an important determinant of renal agenesis or hypoplasia.

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REFERENCES

33. Miettinen OS. Proportion of disease caused or prevented by a given exposure, trial, or intervention. Am J Epidemiol. 1974;99:325–332
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