Published in final edited form as:
Birth Defects Res A Clin Mol Teratol. 2008 July ; 82(7): 519–526. doi:10.1002/bdra.20461.

Maternal Periconceptional Smoking and Alcohol Consumption and Risk for Select Congenital Anomalies

Jagteshwar Grewal[1], **Suzan L. Carmichael**[2,*], **Chen Ma**[2], **Edward J. Lammer**[3], and **Gary M. Shaw**[2]

[1] Division of Epidemiology, Statistics and Prevention Research, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland [2] March of Dimes/ California Research Division, Oakland, California [3] Children's Hospital Oakland Research Institute, Oakland, California

Abstract

BACKGROUND—This study examined the association between maternal smoking and alcohol use (including binge drinking) during the periconceptional period (i.e., 2 months before through 2 months after conception) and the risk of orofacial clefts, NTDs, and conotruncal heart defects in offspring.

METHODS—Data were drawn from a population-based case-control study of fetuses and live-born infants among a cohort of California births between July 1999 and June 2003. The 1,355 cases comprised of 701 orofacial clefts, 337 NTDs, and 323 conotruncal heart defects. Information on smoking and alcohol consumption was obtained via telephone interviews with mothers of 1,355 (80% of eligibles) cases and 700 (77% of eligibles) nonmalformed, live-born controls.

RESULTS—Maternal smoking of five cigarettes or less per day was associated with reduced risks of NTDs (OR 0.7; 95% CI: 0.3, 1.4), whereas the risk associated with higher cigarette consumption was lower for conotruncal heart defects (OR 0.5; 95% CI: 0.2, 1.2). Maternal intake of alcohol less than 1 day per week was associated with a 1.6- to 2.1-fold higher risk of NTDs (95% CI: 0.9, 2.6), d-transposition of the great arteries (95% CI: 1.1, 3.2), and multiple cleft lip with or without cleft palate (CLP) (95% CI: 0.8, 4.5). Risks associated with more frequent alcohol intake were 2.1 for NTDs (95% CI: 1.1, 4.0) and 2.6 for multiple CLP (95% CI: 1.1, 6.1).

CONCLUSIONS—This study observed that maternal alcohol intake increased the risk for d-transposition of the great arteries, NTDs, and multiple CLP in infants. By contrast, smoking was associated with a lower risk of NTDs and conotruncal heart defects.

Keywords

smoking; alcohol; drinking; conotruncal heart defect; NTDs; clefts; congenital anomalies; pregnancy

INTRODUCTION

Numerous human studies have investigated potential teratogenic effects of maternal smoking during pregnancy, with conflicting findings. One segment of the literature indicates that

*Correspondence to: Suzan Carmichael, March of Dimes California Research Division, Children's Hospital Oakland Research Institute, 5700 Martin Luther King Jr. Way, Oakland, CA 94609. SCarmichael@marchofdimes.com.

Presented at the 47th Annual Meeting of the Teratology Society, Pittsburgh, PA, June 23–28, 2007.

Presented at the 20th Annual Meeting of the Society for Pediatric and Perinatal Epidemiologic Research, Boston, MA, June 18–19, 2007.

smoking during pregnancy increases the risk of delivering a child with orofacial clefts (Kelsey et al., 1978; Khoury et al., 1987, 1989; Shaw et al., 1996b; Chung, et al., 2000). Other research, however, shows that exposure to cigarette smoke during pregnancy is not associated with an increased risk of clefts (Evans et al., 1979; Werler et al., 1990; Lieff et al., 1999; Romitti et al., 2007). In addition, some studies have suggested that periconceptional maternal smoking increases the risk of NTDs in offspring (Kelsey et al., 1978; Evans et al., 1979; Suarez et al., 2007), while others have shown no relation (McDonald et al., 1992; Wasserman et al., 1996) or even a reduced effect (Shaw et al., 1996a). Similarly, the few epidemiological studies that examined the association between maternal smoking and conotruncal heart defects offered mixed results: two studies indicated an increased risk (Kelsey et al., 1978; Shaw et al., 1992) while two others reported no association (Adams et al., 1989; Wasserman et al., 1996).

Meanwhile, the adverse impact of periconceptional alcohol consumption on the growth and mental development of the fetus—collectively referred to as fetal alcohol syndrome—is well established (Jones et al., 1973; Hanson et al., 1976, 1978; Riley et al., 2003). Yet the association of alcohol consumption with major congenital anomalies, especially those not characteristic of fetal alcohol syndrome, remains a matter of debate. Some epidemiological evidence indicates that the relationship between alcohol use during pregnancy and congenital malformations varies by the amount of alcohol intake. One population-based case-control study showed that even a low level of alcohol consumption during pregnancy was significantly associated with an elevated risk of orofacial clefts in the offspring (Munger et al., 1996). Other studies have concluded instead that there was no significant association between low levels of maternal alcohol intake and increased risk of oral clefts (Werler et al., 1991; Shaw and Lammer, 1999; Meyer et al., 2003). Two of these studies (Werler et al., 1991; Shaw and Lammer, 1999), however, reported an increased probability of cleft lip in the offspring of women who engaged in binge drinking—that is, consumed five or more drinks per drinking occasion—during pregnancy. Likewise, there is considerable uncertainty regarding the role of alcohol intake during pregnancy in the development of conotruncal heart defects. At least three studies have shown that maternal alcohol consumption results in a moderately elevated risk of such defects (Shaw et al., 1992; Tikkanen and Heinonen, 1992; Carmichael et al., 2003), whereas two other studies found no association (Adams et al., 1989; Ferencz et al., 1997). The few epidemiologic studies that have evaluated the potential association between alcohol intake during early pregnancy and NTDs have concluded that such consumption did not increase the risk of defects in infants (Mills and Graugard, 1987; McDonald et al., 1992; Shaw et al., 1996a; Suarez et al., 2007).

Our research, in turn, employs data from a large population-based case-control study in California to assess the association between the risk of NTDs, conotruncal heart defects, or orofacial clefts in offspring and periconceptional maternal smoking and alcohol consumption, including binge drinking. A key motivation for this study is to address an important gap in the published literature concerning the association between smoking and alcohol intake and birth defects by examining the simultaneous impact of these exposures on risks for three major congenital anomalies. We also wanted to re-evaluate these relationships in the context of the substantial decline in the prevalence of the two exposures over the recent decades: the share of the adult population in the US that smoked dropped by 38% between 1979 and 2004 (NCHS, 2006), while the share that consumed alcohol dropped by 13% between 1978 and 2003 (NIAAA, 2004).

MATERIALS AND METHODS

Data for the analyses were drawn from a population-based case-control study that included deliveries that had estimated due dates (EDDs) between July 1999 and June 2004. Information on all live-born, still-born (i.e., fetal deaths at greater than 20 weeks gestation), and prenatally

diagnosed, electively terminated cases that occurred to mothers residing in Los Angeles, San Francisco, and Santa Clara counties was ascertained from multiple hospital reports and medical records and reviewed by a clinical geneticist to determine eligibility. The 1,698 cases included cleft palate (CP), cleft lip with or without cleft palate (CLP), spina bifida, anencephaly, and the conotruncal heart defects d-transposition of the great arteries (dTGA) and tetralogy of Fallot (TOF). Spina bifida encompassed cases of lipomeningocele, meningomyelocele, and myelocystocele. For each conotruncal heart defect case, anatomic features were confirmed by reviewing echocardiography, cardiac catheterization, surgery, or autopsy reports. All cases were further classified as isolated, if there was no concurrent major anomaly, or nonisolated if there was at least one accompanying major, unrelated anomaly. Ascertainment of clefts and NTDs ended with EDDs on June 30, 2003, whereas ascertainment of conotruncal heart cases and controls ended with EDDs on June 30, 2004. Infants with trisomies, 22q11 microdeletions, other unbalanced chromosomal abnormalities, or known single gene disorders were excluded from this study. In addition, 907 nonmalformed, live-born controls were randomly selected from the same birth hospitals to represent the general population from which cases were derived.

Mothers of cases and controls were eligible to be interviewed if they were the biological mother and carried the pregnancy of the selected study subject, were not incarcerated, and if their primary language was English or Spanish. Overall, 1,355 mothers (80% of eligibles) in the case group and 700 mothers (77% of eligibles) in the control group were interviewed. Data were unavailable from 11% of mothers of eligible cases and 12% of mothers of controls who could not be located, and an additional 9% of mothers of cases and 11% of mothers of controls who refused to participate. Interviews were conducted primarily over the telephone in English or Spanish, no earlier than 6 weeks after the EDD. The median time between EDD and interview completion was 10 months for cases and 8 months for controls.

A standardized, computer-based questionnaire was used to elicit detailed information on smoking and alcohol consumption, as well as potential covariates, during the 4 month periconceptional time period, defined as the 2 months before through the 2 months after conception. To assess maternal smoking and alcohol consumption, women were asked to report the average number of cigarettes they smoked per day, how often they consumed alcohol, and the number of drinks they consumed per drinking day, during each month of the periconceptional period. To assess binge drinking, women were asked to estimate the number of days in each of the 4 months that they consumed five or more drinks on one occasion. Maternal smoking, defined as the average number of cigarettes smoked per day, and alcohol intake were analyzed separately for each of the 4 months of the periconceptional period. We examined two indicators of alcohol consumption: (1) the number of drinking days per week and (2) the number of drinks per drinking day. The reference group for the smoking analyses was comprised of women who indicated no smoking during the entire periconceptional period, whereas the reference group for the alcohol consumption analyses consisted of women who indicated no smoking or alcohol consumption during these 4 months.

All data analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC). OR and their corresponding 95% CIs—an estimate of the relative risk associated with maternal smoking and alcohol consumption for each case group—were estimated from logistic regression models. Due to potential heterogeneity of associations across phenotypic subtypes, separate analyses were also conducted for dTGA and TOF (conotruncal heart defects), for spina bifida and anencephaly (NTDs), and for CLP and CP alone. The association of these three major congenital anomalies with the exposures was examined separately for each of the 4 months of the periconceptional period. However, only the results for the first month of pregnancy are reported, because this was considered to be coincident with the most important embryologic time period. Maternal age at the time of conception, body mass index, race/

ethnicity (US-born Hispanic, foreign-born Hispanic, White, Asian, African-American, or other), education (<high school, high school, some college, or ≥4 years of college), gravidity (defined as the total number of previous pregnancies; 0, 1, 2, or >2), employment (yes or no), and intake of folic acid-containing supplements (yes or no) were considered as potential covariates.

RESULTS

The distributions of select maternal characteristics for the four case groups and the controls are presented in Table 1. Approximately half of mothers of both cases and controls were in the range of 25 to 34 years of age, with an average age of approximately 29 years. The maternal race/ethnicity distributions varied by defect—for example, compared to controls, the mothers of NTD and CLP cases were more likely to be foreign-born Hispanics, while the mothers of NTD cases were less likely to be Asian. In addition, mothers of cases with NTDs, CP, and CLP were less likely to have used folic acid-containing supplements during the periconceptional period, relative to the mothers of controls. Lastly, mothers of cases with NTDs were less likely to have completed a high school education, as compared to mothers of controls.

At the start of the periconceptional time period, between 9 and 13% of the mothers in the case groups were classified as smokers, as compared to 11% of the mothers in the control group (Table 1). These percentages dropped steadily over the 4 month study period: smoking during the second month of pregnancy was reported by just 5% of the mothers of the control group and between 1 and 4% of the mothers in the case groups. The proportions that reported alcohol consumption dropped from 27–28% at 2 months prior to pregnancy to 6–7% during the second month of pregnancy. Binge drinking also declined: the percentage of mothers who reported consuming five drinks or more at one occasion fell from a range of 3–9% at the start of the periconceptional period to around 1% at the end.

Table 2 summarizes the unadjusted risk estimates associated with maternal smoking—classified as none, ≤5 cigarettes per day, and >5 cigarettes per day—during the first month of pregnancy. Among women who reported smoking five cigarettes or less per day, elevated risks were not observed for most defects, except for modest, but imprecise (as indicated by the wide confidence bands), increased risks for TOF (OR 1.6; 95% CI: 0.8, 3.2), multiple CP (OR 1.5; 95%CI: 0.4, 5.2), and multiple CLP (OR 1.4; 95% CI: 0.4, 4.8). By contrast, results for smoking five cigarettes or less per day and NTDs suggested an inverse risk, both when examined as a single group (OR 0.7; 95% CI: 0.3, 1.4) and when divided into the phenotypes anencephaly (OR 0.4; 95% CI: 0.1, 1.5) and spina bifida (OR 0.8; 95% CI: 0.3, 1.9). Similar results were observed among women who smoked more than five cigarettes per day for conotruncal heart defects as a group (OR 0.5; 95% CI: 0.2, 1.2) and for the phenotypes dTGA (OR 0.4; 95% CI: 0.1, 1.7) and TOF (OR 0.5; 95% CI: 0.2, 1.7). All of the 95% confidence bands associated with the ORs contained one and were wide, underlining the imprecision of the risk estimates. The results for the other 3 months of the periconceptional period were generally similar to those for the first month of the pregnancy (data not shown). The data were too sparse to simultaneously adjust for all the covariates in multivariable models; instead, single variable control was undertaken. Adjustment of the risk estimates for covariates did not yield results that were sufficiently different to change the interpretation associated with the crude risk estimates reported in Table 2 (data not shown).

The unadjusted analysis showed that women who consumed alcohol less than once a week during the first month of their pregnancy had a 1.5-fold greater risk (95% CI: 1.0, 2.2), relative to nondrinkers, of delivering infants with conotruncal heart defects (Table 3). This increase was attributed largely to the phenotypic subgroup dTGA, for which nearly a twofold elevated risk was observed (OR 1.9; 95% CI: 1.1, 3.2). Similarly, the risk of delivering infants with

isolated CP was somewhat elevated (OR 1.4; 95% CI: 0.8, 2.5), while the risk of offspring with multiple CLP was 1.9-fold higher (95% CI: 0.8, 4.5). Drinking more frequently—that is, consuming alcohol at least once a week—was associated with elevated risk only for multiple CLP (OR 2.6; 95% CI: 1.1, 6.1). This elevated, albeit imprecise, risk of multiple CLP was also observed with respect to binge drinking, defined as consuming five or more drinks per drinking occasion, during the first month of pregnancy (OR 2.3; 95% CI: 0.7, 7.0). The data were too sparse for binge drinking to simultaneously adjust for all the covariates in multivariable models; instead, single variable control was undertaken. Controlling for the individual covariates did not produce risk estimates that were substantially different from the crude estimates reported in Table 3—all of the adjusted risk estimates changed by less than 12%.

After adjustment for covariates, the risk estimates associated with alcohol consumption during the periconceptional period were similar to the crude estimates reported above, with the exception of NTDs. Relative to non-drinkers, women who consumed alcohol less than once a week during the first month of pregnancy had a 1.6-fold increased risk of delivering infants with NTDs (95% CI: 0.9, 2.6), as compared to an unadjusted OR of 1.1, while women who consumed alcohol once a week or more had a 2.1-fold increased risk (95% CI: 1.1, 4.0), as compared to an unadjusted OR of 1.1. The results for the anencephaly and spina bifida phenotypes showed elevated risks that were similar to those reported for all NTD cases combined (data not shown).

We further examined the association between alcohol intake during the periconceptional period and the risk of congenital anomalies using a second index of alcohol consumption, that is, the number of drinks per drinking day, categorized into two groups: one drink and greater than one drink per drinking day. Next, we evaluated the joint distributions of the two indices of alcohol consumption by estimating the risks for each level of drinks per drinking day within each level of drinking days per week. These additional analyses yielded results that were similar to those reported in Table 3 (data not shown).

DISCUSSION

We found that smoking five cigarettes or less per day during the periconceptional period was associated with lower risk of NTDs, spina bifida, and anencephaly, while higher cigarette consumption (i.e., more than five cigarettes per day) was associated with lower risk of conotruncal heart defects, dTGA, and TOF in offspring. We also found that maternal intake of alcohol less than 1 day per week was associated with a 1.6- to 1.9-fold higher risk of NTDs, dTGA, and multiple CLP, while more frequent intake (i.e., at least 1 day per week) was associated with higher risk of NTDs and multiple CLP. Unlike a majority of the previous studies, we evaluated the effects of smoking and alcohol consumption simultaneously. This approach, however, did not yield estimates of risk of congenital anomalies that were substantially different from when these exposures were considered independently.

The decreased risks of NTDs and conotruncal heart defects associated with maternal smoking during the periconceptional period could be indicative of true risks or could be artifactual explained by the modestly elevated risk (i.e., relative risks of less than 1.5) of spontaneous abortion (Risch et al., 1988; Armstrong et al., 1992) among mothers who smoked during pregnancy. Complete ascertainment of NTDs among spontaneous abortions is essentially not possible. Thus, we can not disentangle whether the reduced risk is real or artifact. However, our finding of a reduced risk of NTDs in offspring associated with maternal smoking during the periconceptional period is consistent with the results of Shaw et al. (1996a), who reported risk estimates of 0.9 and 0.7 for mothers who smoked 1–19 cigarettes per day and ≥20 cigarettes per day, respectively. Both of these sets of results are contrary to those in earlier studies that have either reported an increase in the risk of NTDs (Kelsey et al., 1978; Evans et al., 1979;

Suarez et al., 2007) or have showed no association (McDonald et al., 1992; Wasserman et al., 1996). Our finding of a reduced risk of conotruncal heart defects associated with periconceptional smoking of more than five cigarettes per day is inconsistent with two previous studies that reported no association (Adams et al., 1989; Wasserman et al., 1996), and two others that reported ORs of 1.3 for mothers who smoked 20 cigarettes or less per day (Kelsey et al., 1978) and 1.9 for mothers who smoked just 1–9 cigarettes per day (Shaw et al., 1992). As these latter two studies examined conotruncal heart defects as a group and did not report results for the specific phenotypes, they do not offer a basis for comparison of our finding that maternal smoking was associated with a reduced risk of dTGA and TOF. Finally, our finding that maternal smoking during the periconceptional period does not play a significant role the etiology of orofacial clefts, with the possible exception of isolated CP, is supported by three studies (Evans et al., 1979; Werler et al., 1990; Lieff et al., 1999), yet contradicted by several others (Kelsey et al., 1978; Khoury et al., 1987, 1989; Shaw et al., 1996b; Chung et al., 2000; Honein et al., 2007). A number of our estimates of the risk of defects associated with maternal smoking are based on sparse data; therefore, the observed results might alternatively be attributable to random variation.

Our findings of elevated risk associated with periconceptional alcohol consumption are bolstered by experimental research that has suggested tenable mechanisms between alcohol and abnormal development (Pullarkat, 1991; Shean and Duester, 1993). Indeed, several studies have examined the link between maternal alcohol consumption and the risk for conotruncal heart defects in offspring, with conflicting findings. A population-based case-control study of California births between 1987 and 1988 noted that the risk of conotruncal heart defects in offspring was moderately elevated among women who consumed alcoholic beverages during the periconceptional period (Carmichael et al., 2003). These results agree with two earlier studies (Shaw et al., 1992; Tikkanen and Heinonen, 1992), but are contradicted by two others that found no association (Adams et al., 1989; Ferencz et al., 1997). Our study findings are consistent with the former research: we observed a risk of conotruncal heart defects—particularly dTGA—that was nearly twofold higher among infants whose mothers reported alcohol consumption during the periconceptional period.

The potential association between alcohol intake during early pregnancy and NTDs was first described in a clinical study 25 years ago (Freidman, 1982). Our results, however, are consistent with several subsequent epidemiologic studies (Mills and Graubard, 1987; McDonald et al., 1992; Shaw et al., 1996a), each of which found no significant increase in NTD risk associated with maternal alcohol use during early pregnancy. Similarly, our finding that maternal alcohol consumption during the periconceptional period was not associated with an elevated risk of most of the cleft phenotypes is generally consistent with previous studies (Werler et al., 1991; Shaw and Lammer, 1999). We did observe an increase in the risk of multiple CLP, unlike Munger et al. (1996), who found an effect only for isolated CLP. Our findings also suggested that binge drinking is associated with a higher risk of multiple CLP, but not other cleft phenotypes, which is in contrast to the findings of Werler et al. (1991) and Shaw and Lammer (1999). With the exception of isolated CLP (where no association was observed), however, our study lacked power to accurately estimate risks of clefts associated with binge drinking.

Any similarities and differences in results should be considered with caution given variation across studies in the definition of the periconceptional period, the methods for quantifying smoking and alcohol consumption, and the time period over which data were collected (and as a result, the interval between exposure and interview). For example, given the low prevalence of smoking in our study population, we were unable to replicate the broad smoking categories that were employed in previous studies (Shaw et al., 1992; Wasserman et al., 1996; Suarez et al., 2007; Honein et al., 2007), thus making direct comparison difficult. Similarly, we cannot easily compare our findings on alcohol consumption with previous studies, as we considered

both the frequency (number of drinking days per week) and amount of alcohol consumption (number of drinks per drinking day), whereas several of the previous studies used a more limited classification of alcohol intake, for example, simply distinguishing between those who consumed alcohol and those who did not.

Another important consideration is the decline in the prevalence of smoking and alcohol consumption in the US during the past few decades: the share of the adult population in the US that smoked dropped by 38% between 1979 and 2004 (NCHS, 2006), while the share that consumed alcohol dropped by 13% between 1978 and 2003 (NIAAA, 2004). Among pregnant mothers, the decline in smoking prevalence was even steeper: 48% between 1989 (the first year for which data were reported) and 2004 (NCHS, 2006). According to data from two cross-sectional National Health and Nutrition Examination Surveys conducted in 1988–1994 and 1999–2002, the average number of cigarettes smoked per day fell by nearly 15% during this time period (O'Connor et al., 2006). The sales of high-tar and -nicotine delivery cigarettes have also dropped significantly since 1978, whereas sales of medium- and low-delivery cigarettes increased over the same time frame (NIAAA, 2004). Although the overall prevalence of smoking and alcohol consumption has declined, our results—that maternal alcohol consumption during the periconceptional period continues to increase risk of NTDs, dTGA, and multiple CLP, whereas maternal smoking decreases risk for NTDs and conotruncal heart defects—are consistent with earlier studies that were conducted when these exposures were more common.

A further issue to bear in mind is the potential impact of reporting bias. The behaviors that mothers of cases report could be influenced by increased public awareness of the potential teratogenic effects of smoking and alcohol consumption during pregnancy. Mothers may be inclined to underestimate their exposures, denying a possible causal role. On the other hand, they may overestimate their exposures, believing there is a causal role. Previous studies have suggested that for many chronic exposures, reporting bias is likely to be minimal in studies of congenital anomalies (Werler et al., 1989; Swan et al., 1992; Khoury et al., 1994). To help gauge whether such a bias exists in our study, we examined data from the National Birth Defects Prevention Study (NBDPS), an ongoing, multistate, case-control study of environmental and genetic risk factors for major birth defects. According to NBDPS data from 1999–2004, the percentage of control mothers in California who smoked ranged from 12% 2 months before pregnancy to 8% 2 months after conception—versus 11 and 5%, respectively, in our study. The prevalence of alcohol intake among the NBDPS control mothers ranged from 22% 2 months before pregnancy to 8% 2 months after conception—versus 27 and 6%, respectively, in our study. The comparison, therefore, reveals only modest differences in the prevalence of these exposures and offers no specific evidence that the mothers in our study may have over- or under-reported smoking and alcohol consumption.

Finally, we also cannot rule out residual confounding as a possible explanation for our findings. Although all of the analyses were ultimately adjusted for several covariates known to be associated with both exposures and the selected birth defects, it is possible that the omission of additional unmeasured confounders contributed to our results.

In summary, this large, population-based, case-control study revealed that even limited maternal alcohol intake during the periconceptional period was associated with a higher risk of select congenital anomalies—especially NTDs, dTGA, and multiple CLP—in offspring. By contrast, no such effects were observed in regards to maternal smoking, which was actually associated with a lower risk of conotruncal heart defects and NTDs in offspring.

Acknowledgments

Grant sponsor: NIH; Grant number: R01 HD 42538-03.

Grant sponsor: Centers for Disease Control and Prevention; Grant number: U50/CCU913241.

Grant sponsor: California Tobacco-Related Diseases Research Program; Grant number: 13RT-0109.

References

Adams MM, Mulinare J, Dooley K. Risk factors for conotruncal cardiac defects in Atlanta. J Am Coll Cardiol 1989;14:432–442. [PubMed: 2787814]

Armstrong BG, McDonald AD, Sloan M. Cigarette, alcohol, and coffee consumption and spontaneous abortion. Am J Public Health 1992;82:85–87. [PubMed: 1536340]

Carmichael SL, Shaw GM, Yang W, et al. Maternal periconceptional alcohol consumption and risk for conotruncal heart defects. Birth Defects Res A Clin Mol Teratol 2003;67:875–878. [PubMed: 14745941]

Chung KC, Kowalski CP, Kim HM, et al. Maternal cigarette smoking during pregnancy and the risk of having a child with cleft lip/palate. Plast Reconstr Surg 2000;105:485–491. [PubMed: 10697150]

Evans DR, Newcombe RG, Campbell H. Maternal smoking habits and congenital malformations: a population study. Br Med J 1979;2:171–173. [PubMed: 466337]

Ferencz, C.; Loffredo, CA.; Correa-Villasenor, A., et al. Genetic and environmental risk factors of major cardiovascular malformations: the Baltimore-Washington Infant Study 1981–1989. Armonk, NY: Futura Publishing Company, Inc; 1997. p. 59-102.

Friedman JM. Can maternal alcohol ingestion cause neural tube defects? J Pediatr 1982;101:232–234. [PubMed: 7097418]

Hanson JW, Jones KL, Smith DW. Fetal alcohol syndrome. Experience with 41 patients. JAMA 1976;235:1458–1460. [PubMed: 946444]

Hanson JW, Streissguth AP, Smith DW. The effects of moderate alcohol consumption during pregnancy on fetal growth and morphogenesis. J Pediatr 1978;92:457–460. [PubMed: 632992]

Honein MA, Rasmussen SA, Reefhuis J, et al. Maternal smoking and environmental tobacco smoke exposure and the risk of orofacial clefts. Epidemiol 2007;18:226–233.

Jones KL, Smith DW, Ulleland CN, et al. Pattern of malformation in offspring of chronic alcoholic mothers. Lancet 1973;1:1267–1271. [PubMed: 4126070]

Kelsey JL, Dwyer T, Holford TR, et al. Maternal smoking and congenital malformations: an epidemiological study. J Epidemiol Community Health 1978;32:102–107. [PubMed: 355285]

Khoury MJ, Gomez-Farias M, Mulinare J. Does maternal cigarette smoking during pregnancy cause cleft lip and palate in offspring? Am J Dis Child 1989;143:333–337. [PubMed: 2644816]

Khoury MJ, James LM, Erickson JD. On the use of affected controls to address recall bias in case-control studies of birth defects. Teratology 1994;49:273–281. [PubMed: 8073366]

Khoury MJ, Weinstein A, Panny S, et al. Maternal cigarette smoking and oral clefts: a population-based study. Am J Public Health 1987;77:623–625. [PubMed: 3565662]

Lieff S, Olshan AF, Werler M, et al. Maternal cigarette smoking during pregnancy and risk of oral clefts in newborns. Am J Epidemiol 1999;150:683–694. [PubMed: 10512422]

McDonald AD, Armstrong BG, Sloan M. Cigarette, alcohol, and coffee consumption and congenital defects. Am J Public Health 1992;82:91–93. [PubMed: 1536342]

Meyer KA, Werler MM, Hayes C, et al. Low maternal alcohol consumption during pregnancy and oral clefts in offspring: the Slone Birth Defects Study. Birth Defects Res A Clin Mol Teratol 2003;67:509–514. [PubMed: 14565622]

Mills JL, Graubard BI. Is moderate drinking during pregnancy associated with an increased risk for malformations? Pediatrics 1987;80:309–314. [PubMed: 3627880]

Munger RG, Romitti PA, Daack-Hirsch S, et al. Maternal alcohol use and risk of orofacial cleft birth defects. Teratology 1996;54:27–33. [PubMed: 8916367]

National Center for Health Statistics. Health, United States, 2006 (with Chartbook on Trends in the Health of Americans). Hyattsville, MD: US Government Printing Office; 2006.

National Institute on Alcohol Abuse and Alcoholism (NIAAA). Percent who drink beverage alcohol by gender, 1939–2003. 2004 [accessed on August 16, 2007]. (http://www.niaaa.nih.gov/Resources/DatabaseResources/QuickFacts/AlcoholConsumption/PercentAlcoholGender.htm

O'Connor RJ, Giovino GA, Kozlowski LT, et al. Changes in Nicotine Intake and Cigarette Use Over Time in Two Nationally Representative Cross-Sectional Samples of Smokers. Am J Epidemiol 2006;164:750–759. [PubMed: 16887891]

Pullarkat RK. Hypothesis: prenatal ethanol-induced birth defects and retinoic acid. Alcohol Clin Exp Res 1991;15:565–567. [PubMed: 1877745]

Riley EP, Mattson SN, Li TK, et al. Neurobehavioral consequences of prenatal alcohol exposure: an international perspective. Alcohol Clin Exp Res 2003;27:362–373. [PubMed: 12605086]

Risch HA, Weiss NS, Clarke EA, et al. Risk factors for spontaneous abortion and its recurrence. Am J Epidemiol 1988;128:420–430. [PubMed: 3273482]

Romitti PA, Sun L, Honein MA, et al. Maternal periconceptional alcohol consumption and risk of orofacial clefts. Am J Epidemiol 2007;166:775–785. [PubMed: 17609516]

Shaw GM, Lammer EJ. Maternal periconceptional alcohol consumption and risk for orofacial clefts. J Pediatr 1999;134:298–303. [PubMed: 10064665]

Shaw GM, Malcoe LH, Swan SH, et al. Congenital cardiac anomalies relative to selected maternal exposures and conditions during early pregnancy. Eur J Epidemiol 1992;8:757–760. [PubMed: 1426180]

Shaw GM, Velie EM, Morland KB. Parental recreational drug use and risk for neural tube defects. Am J Epidemiol 1996a;144:1155–1160. [PubMed: 8956628]

Shaw GM, Wasserman CR, Lammer EJ, et al. Orofacial clefts, parental cigarette smoking, and transforming growth factor-alpha gene variants. Am J Hum Genet 1996b;58:551–561. [PubMed: 8644715]

Shean ML, Duester G. The role of alcohol dehydrogenase in retinoic acid homeostasis and fetal alcohol syndrome. Alcohol Alcohol Suppl 1993;2:51–56. [PubMed: 7748347]

Suarez L, Felkner M, Brender JD, et al. Maternal Exposures to Cigarette Smoke, Alcohol, and Street Drugs and Neural Tube Defect Occurrence in Offspring. Matern Child Health J. 2007 [Epub ahead of print].

Swan SH, Shaw GM, Shulman J. Reporting and selection bias in case-control studies of congenital malformations. Epidemiol 1992;3:356–363.

Tikkanen J, Heinonen OP. Risk factors for conal malformations of the heart. Eur J Epidemiol 1992;8:48–57. [PubMed: 1572431]

Wasserman CR, Shaw GM, O'Malley CD, et al. Parental cigarette smoking and risk for congenital anomalies of the heart, neural tube, or limb. Teratology 1996;53:261–267. [PubMed: 8864168]

Werler MM, Lammer EJ, Rosenberg L, et al. Maternal cigarette smoking during pregnancy in relation to oral clefts. Am J Epidemiol 1990;132:926–932. [PubMed: 2239907]

Werler MM, Lammer EJ, Rosenberg L, et al. Maternal alcohol use in relation to selected birth defects. Am J Epidemiol 1991;134:691–698. [PubMed: 1951274]

Werler MM, Pober BR, Nelson K, et al. Reporting accuracy among mothers of malformed and nonmalformed infants. Am J Epidemiol 1989;129:415–421. [PubMed: 2643303]

Birth Defects Res A Clin Mol Teratol. Author manuscript; available in PMC 2010 April 29.

Table 1

Select Maternal Characteristics (Percent) for Cases and Controls

	Conotruncal heart defect (n=323)	Neural tube defects (n=337)	CP (n=199)	CLP (n=502)	Controls (n=700)
Maternal age (years)					
<20	6.8	10.1	4.0	10.8	12.6
20–24	21.1	21.7	18.6	25.0	22.8
25–29	25.5	24.3	27.1	25.4	23.1
30–34	27.3	28.8	32.7	22.8	25.8
35–39	14.0	12.8	14.6	11.8	12.3
≥39	5.3	2.4	3.0	4.4	3.3
Maternal race/ethnicity					
US-born hispanic	16.7	17.3	19.2	15.7	22.5
Foreign-born hispanic	36.5	49.0	34.3	44.7	38.3
White	28.3	22.4	25.8	20.5	20.9
Black	5.0	3.6	6.6	3.2	7.8
Asian	10.7	5.4	13.6	13.5	9.1
Other	2.8	2.4	0.5	2.4	1.5
Maternal education (years)					
<High school	26.1	42.1	23.5	34.0	29.3
High school	18.9	18.8	20.9	22.7	24.2
Some college	24.8	19.7	27.0	23.9	22.1
≥Bachelor’s degree	30.2	19.4	28.6	19.3	24.5
Maternal employment					
Yes	62.7	57.3	70.2	62.0	60.2
Gravidity					
0	23.9	23.4	26.7	26.5	29.6
1	26.3	25.2	26.1	26.1	27.0
2	20.7	21.4	21.6	20.3	19.6
>2	29.1	30.0	25.6	27.1	23.8
Intake of folic acid-containing supplements					
Yes	61.5	54.0	57.8	55.3	61.2
Maternal smoking					

	Conotruncal heart defect (n=323)	Neural tube defects (n=337)	CP (n=199)	CLP (n=502)	Controls (n=700)
B2	8.8	8.6	9.6	12.5	10.6
B1	8.4	7.1	8.6	11.9	10.3
P1	5.9	3.3	5.6	8.8	7.7
P2	3.1	1.2	3.0	4.2	4.6
Maternal alcohol consumption					
B2	26.9	28.4	28.1	27.0	27.1
B1	28.8	27.5	26.7	26.6	26.3
P1	19.1	17.9	17.4	18.4	16.7
P2	6.6	6.9	5.6	6.7	5.6
Maternal binge drinking[a]					
B2	4.0	3.0	4.5	8.6	6.3
B1	5.6	5.0	4.0	5.2	6.3
P1	3.7	2.4	1.0	4.6	4.0
P2	0.6	1.2	0.5	1.2	1.3

CP, cleft palate; CLP, cleft lip with or without cleft palate; B2, two months before pregnancy; B1, one month before pregnancy; P1, first month of pregnancy; P2, second month of pregnancy

[a]Binge drinking is defined as consuming five or more drinks per drinking occasion.

Birth Defects Res A Clin Mol Teratol. Author manuscript; available in PMC 2010 April 29.

Birth Defects Res A Clin Mol Teratol. Author manuscript; available in PMC 2010 April 29.

Table 2

Unadjusted Association of Risk of Select Birth Defects with Maternal Smoking (Cigarettes per Day) during the First Month of Pregnancy

	Maternal smoking	Cases	Controls	OR	95% CI
Conotruncal heart defects (n=320)	None	301	639	Reference	
	≤5	14	29	1.0	[0.5, 2.0]
	>5	5	23	0.5	[0.2, 1.2]
dTGA (n=141)	None	137	639	Reference	
	≤5	2	29	0.3	[0.1, 1.4]
	>5	2	23	0.4	[0.1, 1.7]
TOF (n=179)	None	164	639	Reference	
	≤5	12	29	1.6	[0.8, 3.2]
	>5	3	23	0.5	[0.2, 1.7]
Neural tube defects (n=336)	None	325	572	Reference	
	≤5	10	27	0.7	[0.3, 1.4]
	>5	1	21	N/A[a]	N/A[a]
Anencephaly (n=146)	None	143	572	Reference	
	≤5	3	27	0.4	[0.1, 1.5]
	>5	0	21	N/A[a]	N/A[a]
Spina Bifida (n=190)	None	182	572	Reference	
	≤5	7	27	0.8	[0.3, 1.9]
	>5	1	21	N/A[a]	N/A[a]
Isolated CP (n=152)	None	145	572	Reference	
	≤5	5	27	0.7	[0.3, 1.9]
	>5	2	21	0.4	[0.1, 1.6]
Multiple CP (n=46)	None	42	572	Reference	
	≤5	3	27	1.5	[0.4, 5.2]
	>5	1	21	N/A[a]	N/A[a]
Isolated CLP (n=447)	None	409	572	Reference	
	≤5	25	27	1.3	[0.7, 2.3]
	>5	13	21	0.9	[0.4, 1.7]
Multiple CLP (n=50)	None	45	572	Reference	

Maternal smoking	Cases	Controls	OR	95% CI
≤5	3	27	1.4	[0.4, 4.8]
>5	2	21	1.2	[0.3, 5.3]

OR, odds ratio; CI, confidence interval; dTGA, d-transposition of the great arteries; TOF, Tetralogy of Fallot; NTD, neural tube defect; CP, cleft palate; CLP, cleft lip with or without cleft palate.

[a]The OR was not estimated if the number of exposed cases was less than or equal to one. The reference group includes women who reported no smoking during the entire periconceptional period.

Table 3

Unadjusted Association of Risk of Select Birth Defects with Maternal Alcohol Consumption during the First Month of Pregnancy

	Number of drinking days per week			
	0	<1	≥1	Binge drinking[b]
All conotruncal heart defects (n=247)				
Cases	186	42	19	12
Controls	425	66	49	28
OR [95% CI][a]	Reference	1.5 [1.0, 2.2]	0.9 [0.5, 1.5]	1.0 [0.5, 2.0]
dTGA (n=106)				
Cases	76	22	8	6
Controls	425	66	49	28
OR [95% CI][a]	Reference	1.9 [1.1, 3.2]	0.9 [0.4, 2.0]	1.2 [0.5, 3.0]
TOF (n=141)				
Cases	110	20	11	6
Controls	425	66	49	28
OR [95% CI][a]	Reference	1.2 [0.7, 2.0]	0.9 [0.4, 1.7]	0.8 [0.3, 2.0]
All NTDs (n=261)				
Cases	201	34	26	8
Controls	381	58	43	25
OR [95% CI][a]	Reference	1.1 [0.7, 1.8]	1.1 [0.7, 1.9]	0.6 [0.3, 1.4]
Anencephaly (n=116)				
Cases	91	13	12	3
Controls	381	58	43	25
OR [95% CI][a]	Reference	0.9 [0.5, 1.8]	1.2 [0.6, 2.3]	0.5 [0.1, 1.7]
Spina Bifida (n=145)				
Cases	110	21	14	5
Controls	381	58	43	25
OR [95% CI][a]	Reference	1.3 [0.7, 2.2]	1.1 [0.6, 2.1]	0.7 [0.3, 1.9]
Isolated CP (n=107)				
Cases	81	17	9	1
Controls	381	58	43	25
OR [95% CI][a]	Reference	1.4 [0.8, 2.5]	1.0 [0.5, 2.1]	N/A[c]
Multiple CP (n=34)				
Cases	26	5	3	1
Controls	381	58	43	25
OR [95% CI][a]	Reference	1.3 [0.5, 3.4]	1.0 [0.3, 3.5]	N/A[c]
Isolated CLP (n=340)				
Cases	265	44	31	19
Controls	381	58	43	25
OR [95% CI][a]	Reference	1.1 [0.7, 1.7]	1.0 [0.6, 1.7]	1.1 [0.6, 2.0]

	Number of drinking days per week			
	0	<1	≥1	Binge drinking[b]
Multiple CLP (n=43)				
Cases	27	8	8	4
Controls	381	58	43	25
OR [95% CI][a]	Reference	1.9 [0.8, 4.5]	2.6 [1.1, 6.1]	2.3 [0.7, 7.0]

OR, odds ratio; CI: confidence interval; dTGA, d-transposition of the great arteries; TOF, Tetralogy of Fallot; NTD, neural tube defects; CP, cleft palate; CLP, cleft lip with or without cleft palate.

[a]The reference group includes women who reported no smoking and no alcohol consumption during the entire periconceptional period.

[b]Binge drinking is defined as consuming five or more drinks per drinking occasion.

[c]The OR was not estimated if the number of exposed cases was less than or equal to one.