HHS Public Access

Author manuscript

Birth Defects Res A Clin Mol Teratol. Author manuscript; available in PMC 2018 July 12.

Published in final edited form as:

Birth Defects Res A Clin Mol Teratol. 2011 July ; 91(7): 623–630. doi:10.1002/bdra.20823.

Associations Between Periconceptional Alcohol Consumption and Craniosynostosis, Omphalocele, and Gastroschisis

Sandra Richardson[1,*], **Marilyn L. Browne**[1,2], **Sonja A. Rasmussen**[3], **Charlotte M. Druschel**[1,2], **Lixian Sun**[4,5], **Ethylin Wang Jabs**[6], and **Paul A. Romitti**[4] **National Birth Defects Prevention Study**

[1]Congenital Malformations Registry, Bureau of Environmental and Occupational Epidemiology, New York State Department of Health, Troy, New York

[2]Department of Epidemiology and Biostatistics, School of Public Health, University at Albany, Rensselaer, New York

[3]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia

[4]Department of Epidemiology, College of Public Health, The University of Iowa, Iowa City, Iowa

[5]Dana-Farber Cancer Institute, Boston, Massachusetts

[6]Department of Genetics and Genomic Sciences, Department of Pediatrics, and Department of Developmental and Regenerative Biology, Mount Sinai School of Medicine, New York, New York

Abstract

BACKGROUND: Alcohol consumption during pregnancy is known to be associated with certain birth defects, but the risk of other birth defects is less certain. The authors examined associations between maternal alcohol consumption during pregnancy and craniosynostosis, omphalocele, and gastroschisis among participants in the National Birth Defects Prevention Study, a large, multicenter case–control study.

METHODS: A total of 6622 control infants and 1768 infants with birth defects delivered from 1997–2005 were included in the present analysis. Maternal alcohol consumption was assessed as any periconceptional consumption (1 month prepregnancy through the third pregnancy month), and by quantity-frequency, duration, and beverage type. Alcohol consumption throughout pregnancy was explored for craniosynostosis since the period of development may extend beyond the first trimester. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were estimated using unconditional logistic regression analysis. OR were adjusted for age, race/ethnicity, and state of residence at time of infant's birth. Gastroschisis OR were also adjusted for periconceptional smoking.

RESULTS: Periconceptional alcohol consumption and craniosynostosis showed little evidence of an association (OR 5 0.92; CI: 0.78–1.08), but alcohol consumption in the second (OR 5 0.65; CI: 0.47–0.92) and third trimesters (OR 5 0.68; CI: 0.49–0.95) was inversely associated with

[*]Correspondence to: Sandra Richardson, Bureau of Environmental and Occupational Epidemiology, New York State Department of Health, 547 River Street, Room 200, Troy, NY 12180-2216. sdr06@health.state.ny.us.

craniosynostosis. Periconceptional alcohol consumption was associated with omphalocele (OR 5 1.50; CI: 1.15–1.96) and gastroschisis (OR 5 1.40; CI: 1.17–1.67).

CONCLUSIONS: Results suggest that maternal periconceptional alcohol consumption is associated with omphalocele and gastroschisis, and second and third trimester alcohol consumption are inversely associated with craniosynostosis.

Keywords

alcohol drinking; case-control studies; congenital abnormalities; craniosynostosis; gastroschisis; omphalocele

INTRODUCTION

It is known that alcohol consumption during pregnancy may be harmful to the fetus, resulting in certain birth defects and other adverse pregnancy outcomes (Spagnolo, 1993; Maier and West, 2001; Day 2004; Grewal et al., 2008). Despite this, alcohol consumption is relatively common during pregnancy (Centers for Disease Control and Prevention 2004; Edwards and Werler, 2006; Centers for Disease Control and Prevention 2009; Ethen et al., 2009) and in particular during the early months of pregnancy, when a woman may be unaware of her pregnancy (Edwards and Werler, 2006) and when some structural defects occur (Cohen 1993; Blais et al., 1995; Morriss-Kay and Wilkie, 2005; Stevenson et al., 2009). Nevertheless, the risks of some birth defects have not been well studied. More evidence is needed about the risks for birth defects associated with various amounts and patterns of alcohol intake. For these reasons, it is important to study maternal alcohol use and birth defects that occur early in pregnancy.

Relatively few studies have considered the relationship between maternal alcohol consumption and three birth defects thought to occur in early pregnancy: craniosynostosis, omphalocele, or gastroschisis. Events leading to premature fusion of the cranial sutures (craniosynostosis) may happen early in pregnancy but could also occur throughout pregnancy (Cohen 1993; Morriss-Kay and Wilkie, 2005). Omphalocele and gastroschisis are birth defects that develop early in pregnancy when the abdominal wall structures are forming (Blais et al., 1995; Stevenson et al., 2009). Alderman et al. (1994) did not find statistically significant associations between maternal alcohol consumption and craniosynostosis. However, Zeiger et al. (2002) found a statistically significant inverse association between maternal alcohol consumption and sagittal craniosynostosis. Werler et al. (1992) noted statistically significant age-adjusted relative risks between alcohol consumption during the first 4 lunar months of pregnancy and gastroschisis for both ≥six drinks per week and ≥five drinks at one time. Statistically significant crude associations between maternal alcohol consumption and gastroschisis were reported but alcohol consumption was not retained in multivariate analyses by Torfs et al. (1994). Using National Birth Defects Prevention Study (NBDPS) data through 2003, Bird et al. (2009) examined a range of demographic and environmental risk factors for omphalocele and gastroschisis, and found significantly elevated associations between any periconceptional maternal alcohol consumption and omphalocele and gastroschisis. Additional years of NBDPS data have increased the numbers of case infants with omphalocele or gastroschisis, allowing for a more detailed analysis of

maternal alcohol consumption. The aim of this study was to examine risks of craniosynostosis, omphalocele, and gastroschisis in relation to periconceptional maternal alcohol consumption and in particular in relation to varying quantity, binge drinking, and number of months of alcohol intake.

MATERIALS AND METHODS

Study Population

The NBDPS is a large ongoing population-based case–control study (Yoon et al., 2001). The NBDPS has study centers located in Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah. The NBDPS was approved by institutional review boards at each study center. Overall NBDPS participation rates of mothers with an estimated date of delivery (EDD) through December 2005 were 67% for mothers of control infants, and 73%, 71%, and 68% for mothers of infants with craniosynostosis, omphalocele, and gastroschisis, respectively. Maternal interviews were conducted between 6 weeks and 24 months after the EDD using a computer-assisted telephone interview (Yoon et al., 2001). The current analysis included 1768 case and 6622 control infants born on or after October 1, 1997, with an EDD through December 31, 2005, for whom there was information on maternal periconceptional alcohol exposure. We defined periconceptional as 1 month before pregnancy through the third month of pregnancy.

Case Definitions

Case infants included live births from all study centers, stillbirths from all study centers, except New Jersey, and elective terminations from all study centers, except New Jersey and Massachusetts. Data abstracted from medical records were reviewed by clinical geneticists to ensure that standardized case definitions were met. Infants with craniosynostosis, omphalocele, or gastroschisis were included in the current analysis. Craniosynostosis, premature closure of one or more cranial sutures, was identified based on postnatal imaging, surgical correction, or histopathology on autopsy. Omphalocele was identified based on presence of an anterior abdominal wall defect with herniation of some abdominal contents into the umbilical stalk, or prenatal high resolution ultrasound. Gastroschisis was identified based on the presence of an abdominal wall defect lateral to and separate from the umbilicus, with herniation of some abdominal contents and absence of protective tissue, or prenatal high resolution ultrasound. Case infants with a single-gene disorder or chromosomal anomaly were excluded from the study. Clinical geneticists further classified case infants as having isolated (no additional major defects) or multiple defects (more than one unrelated major defect) (Rasmussen et al., 2003). Infants with a complex sequence (a pattern believed to be related to one pathogenic insult, but without a clear primary defect) were excluded from this analysis. An example of a complex sequence is OEIS (omphalocele-exstrophy-imperforate anus-spinal defects). Control infants were nonmalformed live births, randomly selected from either birth records or birth hospitals in the same geographic region as the cases. Excluded for missing exposure data were 14 infants with craniosynostosis, 4 infants with omphalocele, 20 infants with gastroschisis, and 118 control infants. Because diabetes is a known risk factor for many birth defects (Allen et al., 2007; Correa et al., 2008), 8 infants with craniosynostosis, 6 infants with omphalocele, 2

infants with gastroschisis, and 49 control infants with or missing maternal history of prepregnancy diabetes were excluded.

Exposure

Alcoholic drinks were defined as one beer, one glass of wine, one mixed drink, and one shot of liquor. The National Institute on Alcohol Abuse and Alcoholism (2005) provides the following definitions of a standard drink (alcohol %): beer or cooler 12 oz. (5%); malt liquor 8 oz. (7%); table wine 5 oz. (12%); spirits 1.5 oz. (40%). Mothers were asked whether they drank alcoholic beverages during the period 3 months before pregnancy through the date of infant birth. Mothers who responded affirmatively were asked during which months they drank. For each month, they were asked the average number of days they drank, the average number of drinks they had on days they drank, and the highest number of drinks per occasion. Mothers were also asked what type of alcohol (beer, wine, mixed drinks, or shots of liquor) they usually drank. Alcohol exposure was defined as drinking any alcohol during the periconceptional period. Additional periconceptional alcohol exposure groupings were as follows: maximum of average number of drinks per month and binge drinking. For each periconceptional month, average number of drinks per month was calculated from reported average number of drinks per day multiplied by the average number of drinking days per month. Maximum of average drinks per month was the highest number of average drinks per month and was grouped as 0, 1–4, 5–15, 16–30, and >30 drinks per month, categories used in the analysis by Romitti et al. (2007). Based on a 30-day month, these categories correspond to no drinking, and drinking one drink up to once per week, every other day, daily, and more than daily. The National Institute on Alcohol Abuse and Alcoholism definition of binge drinking for women as four or more drinks per occasion (U.S. Department of Health and Human Services, 2004) was used to group drinking as no drinking; drinking (not binge); and binge drinking (≥4 drinks per occasion). Drinking duration values of 0 to 4 indicated the total number of periconceptional months during which alcohol consumption was reported. Based on the proportions of drinking responses in each month, drinking duration given by total periconceptional months of drinking provided a reasonable and inclusive description of drinking behavior, and is a categorization consistent with previous study, allowing comparison across studies. Drink type was grouped into the following categories: none, spirits only (mixed drinks and liquor shots), wine only, beer only, and "more than one type." Maximum of average drinks per month and binge drinking were each examined by drinking duration and drink type. The period of development for craniosynostosis may include the second or third trimester, so we examined maternal alcohol use during these periods as well.

Confounders

Based on previous literature, maternal factors considered for confounding included age; race/ethnicity; state of residence at time of infant's birth; education level; prepregnancy body mass index ([BMI] weight in kilograms/height in meters^2); usual caffeine intake from coffee, tea, soft drinks, and chocolate in the year before pregnancy; periconceptional smoking; folic acid-containing supplement use during 1 month before pregnancy through the first month of pregnancy; parity; maternal fertility treatments or procedures; and periconceptional use of anticonvulsant medications, nonsteroidal anti-inflammatory drugs or

aspirin containing medications, and bronchodilator medications. The evaluation of medications was based on definitions in a drug dictionary provided by Slone Epidemiology Center, Boston University. Folic acid-containing supplement use during 1 month before pregnancy through the first month of pregnancy was evaluated for effect modification on additive and multiplicative scales. Additional analyses were conducted to examine results for isolated and multiple defects, craniosynostosis by suture type involved, singleton births, and infants with no family history of the same defect.

Analysis

Bivariate analyses of each covariate and each defect guided potential confounder selection. Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI). A backward deletion strategy was used to determine confounders retained for each defect. Beginning with a logistic regression model including all literature-based potential confounders (the "full model"), covariates were removed from the model one at a time. The covariate whose removal caused the smallest change in OR was removed from subsequent models. This process was repeated with the remaining covariates to remove from the final model all that did not cause a 10% change in the OR relative to the full model. Covariates causing a ≥10% change in the OR for periconceptional alcohol exposure (no drinking vs any drinking) compared with the full model were retained in final parsimonious models. Maternal age and race/ethnicity are often considered confounders related to birth defects, and mother's state of residence at time of infant's birth is important because of the multicenter design of this study. Each met the confounder definition in our data set for at least one type of birth defect. Therefore, all models controlled for maternal age, race/ethnicity, and mother's state of residence at time of infant's birth. Maternal smoking also met the confounder definition and was retained in gastroschisis models. Maternal age was categorized based on age distribution for craniosynostosis and omphalocele (12–19 years, 20–24 years, 25–29 years, 30–34 years, ≥35 years), and gastroschisis (12–17 years, 18–19 years, 20–24 years, 25–29 years, ≥30 years). Maternal race/ethnicity was defined as non-Hispanic white, non-Hispanic black, Hispanic, or other. Location was defined as the state of residence at time of infant's birth. Periconceptional smoking was defined as any or none. The same set of covariates identified for periconceptional alcohol consumption was used in models for second and third trimester alcohol consumption and craniosynostosis. Analyses were conducted using SAS software version 9.2, copyright 2002–2008 by SAS Institute Inc., Cary, NC.

RESULTS

A total of 1768 infants with birth defects (796 with craniosynostosis, 254 with omphalocele, and 720 with gastroschisis) and 6622 control infants were included in the present analysis. Two case infants had both craniosynostosis and gastroschisis. Compared with controls and infants with other defects in this analysis, mothers of infants with craniosynostosis showed the highest proportion of non-Hispanic white and the lowest proportions of non-Hispanic black and other race/ethnicities. Also, compared with controls and infants with other defects in this analysis, mothers of infants with gastroschisis had the highest proportions of Hispanic race/ethnicity, age <25 years, and periconceptional smoking, and the lowest proportions of

education >12 years, BMI of 25 or more, and use of folic acid-containing supplements. A higher proportion of infants with craniosynostosis were male compared with control infants and infants with omphalocele or gastroschisis (Table 1).

Over half of mothers of both case and control infants reported no alcohol consumption during the periconceptional period. The distributions for periconceptional maximum of average drinks per month, binge drinking, duration of drinking, and type of drink are presented in Table 1. For reference, crude OR between periconceptional alcohol consumption and craniosynostosis, omphalocele, and gastroschisis were 1.01 (CI: 0.87–1.17), 1.45 (1.13–1.87), and 1.17 (1.00–1.37), respectively.

Folic acid-containing supplement use during 1 month before pregnancy through the first month of pregnancy was not found to be effect modifier on the additive or multiplicative scales. Therefore, adjusted OR presented in this paper are not stratified by folic acid-containing supplement use. Adjusted OR showed little evidence of association between periconceptional alcohol consumption and craniosynostosis. Alcohol quantity and frequency measures did not show obvious patterns, but there was a significant inverse association between the longest drinking duration and craniosynostosis (Table 2). Adjusted OR did not reveal statistically significant associations between periconceptional alcohol consumption and craniosynostosis by sagittal, metopic, or coronal suture (data not shown). The adjusted OR between second trimester alcohol consumption and craniosynostosis was 0.65 (CI: 0.47–0.92). For third trimester alcohol consumption and craniosynostosis the adjusted OR was 0.68 (CI: 0.49–0.95).

The adjusted OR showed evidence of association between any periconceptional alcohol consumption and omphalocele. However, a consistent increase in the OR was not seen for increasing maximum of average drinks per month or drinking duration. Both binge drinking and any drinking revealed statistically significant associations for omphalocele, with higher OR for binge drinking (Table 2).

Adjusted OR showed evidence of association between periconceptional alcohol consumption and gastroschisis. Any periconceptional drinking, binge drinking, and most categories of maximum of average drinks per month revealed statistically significant associations for gastroschisis. Drinking duration did not show a monotonic increase in OR for gastroschisis (Table 2). Among singletons and among those without family history of the same defect the adjusted OR between any periconceptional alcohol consumption, maximum of average drinks per month, or binge drinking and each of the three birth defects included in this analysis were similar to those in Table 2. Adjusted OR between any periconceptional alcohol consumption, maximum of average drinks per month, or binge drinking and each of the three birth defects, restricted to isolated or multiple defects, were similar to results in Table 2.

Maximum of average drinks per month and binge drinking by drinking duration (data not shown) did not demonstrate clear dose-response patterns for any of these defects. Nor did maximum of average drinks per month and binge drinking by drink type (data not shown)

reveal patterns notably different from those observed for each drink type overall for these defects.

DISCUSSION

Periconceptional alcohol consumption was found to be associated with omphalocele and gastroschisis. Although periconceptional alcohol consumption showed little evidence of association, second and third trimester alcohol consumption was found to be inversely associated with craniosynostosis. Neither exclusion of multiple births or infants with family history of the same defect, nor stratification by isolated or multiple defect status appreciably changed these findings.

Although most results were not statistically significant, the inverse association between drinking duration or maximum of average number of drinks per month and craniosynostosis displayed an apparent dose-response pattern. This supports the findings of Zeiger et al. (2002) that report a statistically significant inverse association between maternal alcohol consumption and sagittal craniosynostosis (OR 5 0.35; CI: 0.15–0.83). In our study, reduced odds of craniosynostosis were observed for the second and third trimesters but not for the periconceptional period. Alderman et al. (1994) found second and third trimester patterns similar to ours, with relationships between ≥1 oz. ethanol per week and craniosynostosis for the first, second, and third trimester resulting in relative odds of 1.7 (CI: 0.9–3.2), 0.7 (CI: 0.2–2.1), and 0.6 (CI: 0.1–2.2), respectively. Craniosynostosis suture-specific analysis did not produce statistically significant findings, although the association did vary by suture. A possible explanation for the inverse association found between alcohol consumption and craniosynostosis is a relationship between alcohol, retinoic acid, and osteogenesis. Retinoic acid enhances osteogenesis (Song et al., 2005; James et al., 2010), and alcohol intoxication lowers retinoic acid levels (Molotkov and Duester, 2002) in mice. Interactions between alcohol and retinoic acid or genetic factors affecting the metabolism of both alcohol and retinoic acid may influence the risk of craniosynostosis through perturbation of the fine balance of cellular mechanisms involving differentiation, proliferation, and apoptosis (Winograd et al., 1997). Although these potential interactions are of interest in understanding biologic mechanisms, our findings do not suggest that consumption of alcohol during pregnancy is advisable given known neurologic and other risks to the fetus. Another possible explanation for the inverse association between second and third trimester alcohol consumption and craniosynostosis is the result of a healthy drinker effect. Women with known risk for birth defects may choose not to drink alcohol, placing more high-risk women among the unexposed and causing exposure to appear protective. To evaluate the healthy drinker effect, we calculated adjusted OR among women who were not trying to get pregnant. For each of the three defects in this analysis, there was a minimal change in OR of <0.10 for periconceptional alcohol use. Adjusted OR between alcohol consumption and craniosynostosis for the second and third trimesters, among women who were not trying to get pregnant, remained lower than the periconceptional period. This suggests the healthy drinker effect is not present in the periconceptional period and does not completely explain the associations found later in pregnancy.

As expected our adjusted OR between maternal alcohol consumption and omphalocele, 1.50 (CI: 1.15–1.96), and gastroschisis, 1.40 (CI: 1.17–1.67), were very similar to those found by Bird et al. (2009) with adjusted OR between maternal alcohol consumption and omphalocele of 1.53 (CI: 1.04–2.25), and gastroschisis 1.38 (CI: 1.06–1.79). Both studies used NBDPS data, the differences being that our study included 2 additional years of data, evaluated patterns of alcohol consumption in greater detail, and assessed effect modification by folic acid. For omphalocele, we observed a dose-response pattern with binge drinking and a statistically significant elevation in OR for 1 month drinking duration, any periconceptional drinking, beer, and wine. For gastroschisis we observed a dose-response pattern for binge drinking and statistically significant OR for 2 months drinking duration, any periconceptional drinking, drinking (not binge), and binge drinking. OR for gastroschisis were also elevated for spirits, beer, and "more than one type" of alcohol. Although our adjusted OR were lower, our study associations for binge drinking and gastroschisis (OR = 1.53; CI: 1.21–1.92) support the results presented by Werler et al. (1992) reporting significant associations between alcohol consumption during the first 4 lunar months of pregnancy and gastroschisis, for ≥five drinks at one time (OR = 3.2; CI: 1.5–6.7) and six drinks per week (OR = 2.9; CI: 1.1–7.4).

Although birth defects can be difficult to study because of small sample size, the large sample size in this study provided adequate power to assess risks of specific defects in relation to various levels of alcohol exposure. Detailed case definitions and review of cases by clinical geneticists contributed to validity. In addition to large sample size, the broad geographic area represented by the 10 study centers enhances the generalizability of these results.

Study limitations should be considered in interpreting our results. Selection bias is a possibility due to a difference in percent of cases (96%) and controls (100%), which were live births. However, this small difference in live births is unlikely to change our results. There may have been some misclassification of exposure because of respondent interpretation of the size of a beer, glass of wine, shot of liquor, or a mixed drink. Lack of portion size information is a limitation of these data. Even though interviews were conducted within 2 years of expected date of delivery and computer-assisted telephone interview techniques using the same questionnaire for cases and controls were used to minimize recall bias, recall bias is a possible limitation of this study. Undesirable behaviors during pregnancy, such as drinking, smoking, and related activities, may be underreported and may be recalled or reported differently by case and control mothers. However, the association with alcohol use differed for the specific birth defects included in this study, suggesting that recall bias does not strongly influence our findings. Restricting analysis to maternal interviews completed within 1 year of EDD did not substantially alter our results, suggesting that recall bias because of time to interview had little influence. We considered a number of potential confounding variables measured by the NBDPS questionnaire. Nevertheless, uncontrolled confounding due to unmeasured factors remains a possibility. Given the number of statistical tests performed in analyses by quantity-frequency, duration, and type of drink, some statistically significant positive associations would be expected by chance alone. We chose to place less emphasis on individual significant findings and instead focus on patterns and consistency among the results.

It is plausible that alcohol may affect the unique processes of structural development differently for each defect, or possibly interact differently with additional factors that reduce or increase risk specific to each defect. Recent studies indicate that metabolic and genetic factors (Gemma et al., 2006; Haley et al., 2006; Gemma et al., 2007) may impact the effect of alcohol exposure during pregnancy. Further research on alcohol exposure during pregnancy considering metabolic and genetic factors may contribute to understanding the etiology of craniosynostosis, omphalocele, and gastroschisis. Additional research is needed to confirm and explain the biologic mechanisms underlying our results. In conclusion, the results of this study provide evidence that alcohol consumption and in particular binge drinking during the periconceptional period is associated with increased risk of omphalocele and gastroschisis, and alcohol consumption during the second and third trimesters is associated with lowered risk of craniosynostosis. Although these results contribute to understanding the relationships between maternal alcohol consumption and craniosynostosis, omphalocele, and gastroschisis, and suggest a biologic mechanism for craniosynostosis, they also support the warning by U.S. Surgeon General (http://www.surgeongeneral.gov/pressreleases/sg02222005.html) that women who are or may become pregnant should avoid drinking alcohol because alcohol is harmful to the fetus.

ACKNOWLEDGMENT

We thank NBDPS investigators and staff for their contributions to this project.

This work was supported by the Centers for Disease Control and Prevention, grant number 5U01DD000487-02; and in part by Centers for Disease Control and Prevention, grant number 5R01DD000350.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

REFERENCES

Alderman BW, Bradley CM, Greene C. Increased risk of craniosynostosis with maternal cigarette smoking during pregnancy. Teratology. 1994; 50:13–18. [PubMed: 7974250]

Allen VM, Armson BA, Wilson RD. Teratogenicity associated with pre-existing and gestational diabetes. J Obstet Gynaecol Can. 2007; 29:927–944. [PubMed: 17977497]

Bird TM, Robbins JM, Druschel C. Demographic and environmental risk factors for gastroschisis and omphalocele in the National Birth Defects Prevention Study. J Pediatr Surg. 2009; 44:1546–1551. [PubMed: 19635303]

Blaas HG, Eik-Nes SH, Kiserud T. Early development of the abdominal wall, stomach and heart from 7 to 12 weeks of gestation: a longitudinal ultrasound study. Ultrasound Obstet Gynecol. 1995; 6:240–249. [PubMed: 8590186]

Centers for Disease Control and Prevention. Alcohol consumption among women who are pregnant or who might become pregnant— United States, 2002. MMWR Morb Mortal Wkly Rep. 2004; 53:1178–1181. [PubMed: 15614234]

Centers for Disease Control and Prevention. Alcohol use among pregnant and nonpregnant women of childbearing age - United States, 1991-2005. MMWR Morb Mortal Wkly Rep. 2009; 58:529–532. [PubMed: 19478721]

Cohen MM Jr.. Sutural biology and the correlates of craniosynostosis. Am J Med Genet. 1993; 47:581–616. [PubMed: 8266985]

Correa A, Gilboa SM, Besser LM. Diabetes mellitus and birth defects [electronic article]. Am J Obstet Gynecol. 2008; 199:237.e1–239.e9. [PubMed: 18674752]

Day NL, Richardson GA. An analysis of the effects of prenatal alcohol exposure on growth: a teratologic model. Am J Med Genet C Semin Med Genet. 2004; 127C:28–34. [PubMed: 15095469]

Edwards EM, Werler MM. Alcohol consumption and time to recognition of pregnancy. Matern Child Health J. 2006; 10:467–472. [PubMed: 16763772]

Ethen MK, Ramadhani TA, Scheuerle AE. Alcohol consumption by women before and during pregnancy. Matern Child Health J. 2009; 13:274–285. [PubMed: 18317893]

Gemma S, Vichi S, Testai E. Individual susceptibility and alcohol effects:biochemical and genetic aspects. Ann Ist Super Sanita. 2006; 42:8–16. [PubMed: 16801720]

Gemma S, Vichi S, Testai E. Metabolic and genetic factors contributing to alcohol induced effects and fetal alcohol syndrome. Neurosci Biobehav Rev. 2007; 31:221–229. [PubMed: 16908065]

Grewal J, Carmichael SL, Ma C. Maternal periconceptional smoking and alcohol consumption and risk for select congenital anomalies. Birth Defects Res A Clin Mol Teratol. 2008; 82:519–526. [PubMed: 18481814]

Haley DW, Handmaker NS, Lowe J. Infant stress reactivity and prenatal alcohol exposure. Alcohol Clin Exp Res. 2006; 30:2055–2064. [PubMed: 17117971]

James AW, Levi B, Xu Y. Retinoic acid enhances osteogenesis in cranial suture-derived mesenchymal cells: potential mechanisms of retinoid-induced craniosynostosis. Plast Reconstr Surg. 2010; 125:1352–1361. [PubMed: 20134361]

Maier SE, West JR. Patterns and alcohol-related birth defects. Alcohol Res Health. 2001; 25:168–174. [PubMed: 11810954]

Molotkov A, Duester G. Retinol/ethanol drug interaction during acute alcohol intoxication in mice involves inhibition of retinol metabolism to retinoic acid by alcohol dehydrogenase. J Biol Chem. 2002; 277:22553–22557. [PubMed: 11960985]

Morriss-Kay GM, Wilkie AO. Growth of the normal skull vault and its alteration in craniosynostosis: insights from human genetics and experimental studies. J Anat. 2005; 207:637–653. [PubMed: 16313397]

National Institute on Alcohol Abuse and AlcoholismA pocket guide for alcohol screening and brief intervention NIAAA Publications; Rockville, MD: 2005

Rasmussen SA, Olney RS, Holmes LB. Guidelines for case classification for the National Birth Defects Prevention Study. Birth Defects Res A Clin Mol Teratol. 2003; 67:193–201. [PubMed: 12797461]

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

Song HM, Nacamuli RP, Xia W. High-dose retinoic acid modulates rat calvarial osteoblast biology. J Cell Physiol. 2005; 202:255–262. [PubMed: 15389522]

Spagnolo A. Teratogenesis of alcohol. Ann Ist Super Sanita. 1993; 29:89–96. [PubMed: 8129276]

Stevenson RE, Rogers RC, Chandler JC. Escape of the yolk sac: a hypothesis to explain the embryogenesis of gastroschisis. Clin Genet. 2009; 75:326–333. [PubMed: 19419415]

Torfs CP, Velie EM, Oechsli FW. A population-based study of gastroschisis: demographic, pregnancy, and lifestyle risk factors. Teratology. 1994; 50:44–53. [PubMed: 7974254]

U.S. Department of Health and Human ServicesNIAAA council approves definition of binge drinking (NIH Publication No. 04-5346) Office of Research Translation and Communications, NIAAA, NIH, DHHS; Bethesda, MD: 2004

Werler MM, Mitchell AA, Shapiro S. Demographic, reproductive, medical, and environmental factors in relation to gastroschisis. Teratology. 1992; 45:353–360. [PubMed: 1533957]

Winograd J, Reilly MP, Roe R. Perinatal lethality and multiple craniofacial malformations in MSX2 transgenic mice. Hum Mol Genet. 1997; 6:369–379. [PubMed: 9147639]

Yoon PW, Rasmussen SA, Lynberg MC. The National Birth Defects Prevention Study. Public Health Rep. 2001; 116:32S–40S.

Zeiger JS, Beaty TH, Hetmanski JB. Genetic and environmental risk factors for sagittal craniosynostosis. J Craniofac Surg. 2002; 13:602–606. [PubMed: 12218784]

Table 1.

Characteristics of Control Mothers and Mothers of Infants With Selected Birth Defects, National Birth Defects Prevention Study, 1997–2005[a]

	Controls (n = 6622)		Craniosynostosis (n = 796)		Omphalocele (n = 254)		Gastroschisis (n = 720)	
Characteristics	**n**[b]	**%**[c]	**n**[b]	**%**[c]	**n**[b]	**%**[c]	**n**[b]	**%**[c]
Age (y)								
12–19	703	10.6	37	4.7	24	9.5	285	39.6
20–24	1512	22.8	135	17.0	67	26.4	290	40.3
25–29	1754	26.5	216	27.1	55	21.7	94	13.1
30–34	1726	26.1	245	30.8	57	22.4	41	5.7
≥35	927	14.0	163	20.5	51	20.1	10	1.4
Race								
Non-Hispanic white	3957	60.0	596	75.0	149	58.7	387	53.8
Non-Hispanic black	750	11.4	35	4.4	39	15.4	54	7.5
Hispanic	1476	22.4	133	16.7	46	18.1	216	30.0
Other	410	6.2	31	3.9	20	7.9	62	8.6
Education (y)								
<12	1111	16.8	88	11.1	35	13.8	219	30.7
12	1624	24.6	186	23.4	76	29.9	277	38.8
>12	3867	58.6	521	65.5	143	56.3	218	30.5
BMI								
<18.5	354	5.6	37	4.8	12	4.9	62	8.8
18.5–<25	3564	56.0	407	52.3	119	48.8	501	71.1
25–<30	1426	22.4	196	25.2	58	23.8	109	15.5
≥30	1018	16.0	139	17.8	55	22.5	33	4.7
Caffeine[d]								
0–<10 mg/day	1152	17.4	132	16.6	36	14.2	109	15.2
10–<100 mg/day	2390	36.2	264	33.2	87	34.3	264	36.7
100–<200 mg/day	1516	22.9	204	25.7	60	23.6	180	25.0
200–<300 mg/day	833	12.6	85	10.7	40	15.8	76	10.6
≥300 mg/day	719	10.9	110	13.8	31	12.2	90	12.5
Smoking[e]								
No	5375	81.2	651	81.8	204	80.3	455	63.2
Yes	1247	18.8	145	18.2	50	19.7	265	36.8
Folic acid[f]								
No	3066	46.9	307	39.2	118	46.5	431	61.1
Yes	3466	53.1	477	60.8	136	53.5	275	39.0
Parity								
≤2	6015	90.9	713	89.7	238	93.7	696	96.7
>2	606	9.2	82	10.3	16	6.3	24	3.3

	Controls (n = 6622)		Craniosynostosis (n = 796)		Omphalocele (n = 254)		Gastroschisis (n = 720)	
Characteristics	**n**[b]	**%**[c]	**n**[b]	**%**[c]	**n**[b]	**%**[c]	**n**[b]	**%**[c]
Infant sex								
Female	3274	49.5	262	32.9	105	42.3	355	49.4
Male	3343	50.5	534	67.1	143	57.7	363	50.6
Multiple gestation								
No	6418	97.0	749	94.1	233	91.7	705	97.9
Yes	199	3.0	47	5.9	21	8.3	15	2.1
Family history of the same defect								
No	*g*		772	97.0	254	100.0	714	99.2
Yes			24	3.0	0	0.0	6	0.8
Periconceptional alcohol consumption								
No	4171	63.0	500	62.8	137	53.9	426	59.2
Yes	2451	37.0	296	37.2	117	46.1	294	40.8
Periconceptional maximum of average drinks/month								
0	4171	63.2	500	63.0	137	53.9	426	59.7
1–4	1161	17.6	150	18.9	57	22.4	113	15.9
5–15	735	11.1	88	11.1	32	12.6	91	12.7
16–30	340	5.2	38	4.8	19	7.5	36	5.0
>30	195	3.0	18	2.3	9	3.5	48	6.7
Periconceptional binge drinking								
No drinking	4171	63.3	500	63.0	137	53.9	426	59.8
Drinking, not binge	1616	24.5	197	24.8	74	29.1	134	18.8
Binge, ≥4/occasion	805	12.2	97	12.2	43	16.9	152	21.4
Periconceptional drinking duration (months)								
0	4171	63.1	500	62.8	137	54.2	426	59.2
1	1295	19.6	177	22.2	67	26.5	124	17.2
2	743	11.3	82	10.3	30	11.9	115	16.0
3	177	2.7	19	2.4	9	3. 6	29	4.0
4	229	3.5	18	2.3	10	4.0	26	3.6
Periconceptional drink type								
None	4171	63.0	500	62. 9	137	53.9	426	59.3
Spirits only[h]	428	6.5	51	6.4	20	7.9	78	10.9
Wine only	673	10.2	92	11.6	35	13. 8	34	4.7
Beer only	511	7.7	58	7.3	26	10.2	81	11.3
> 1 type	834	12.6	94	11.8	36	14.2	99	13.8

Abbreviations: BMI, body mass index: y, years.

[a] Following exclusion of those with or missing prepregnancy history of type 1 or type 2 diabetes, or missing/invalid valid alcohol data.

[b] Numbers may vary due to misssing data.

[c] Percents may not total 100 due to rounding.

[d] Usual intake during the year before pregnancy based on coffe, tea, soft drink, and chocolate consumption.

[e] During the period 1 month prepregnancy through the third month of pregnancy.

[f] During the period 1 month prepregnancy through the first month of pregnancy.

[g] Controls family history of defect (n, %): craniosynostosis no (6617, 99.92%), yes (5, 0.08%); omphalocele no (6622, 100%), yes (0, 0%); gastroschisis no (6619, 99.95%), yes (3, 0.05%).

[h] Including mixed drinks and liquor shots.

Table 2.

Adjusted Associations Between Periconceptional Alcohol Exposures and Selected Birth Defects, National Birth Defects Prevention Study, 1997–2005[a]

	Controls		Craniosynostosis[b]				Omphalocele[b]				Gastroschisis[c]			
Periconceptional alcohol exposure	**n**	**%**	**n**	**%**	**OR**	**95% CI**	**n**	**%**	**OR**	**95% CI**	**n**	**%**	**OR**	**95% CI**
Alcohol														
No	4150	63.0	500	62.9		referent	137	53.9		referent	425	59.1		referent
Yes	2443	37.1	295	37.1	0.92	0.78-1.08	117	46.1	**1.50**	**1.15–1.96**	294	40.9	**1.40**	**1.17–1.67**
Maximum of average drinks/month														
0	4150	63.1	500	63.1		referent	137	53.9		referent	425	59.6		referent
1–4	1154	17.6	149	18.8	1.00	0.82–1.22	57	22.4	**1.55**	**1.12–2.14**	113	15.8	**1.30**	**1.02–1.64**
5–15	734	11.2	88	11.1	0.89	0.69–1.14	32	12.6	1.39	0.93–2.09	91	12.8	**1.51**	**1.15–1.97**
16–30	340	5.2	38	4.8	0.79	0.56–1.14	19	7.5	**1.73**	**1.05–2.87**	36	5.1	1.12	0.75–1.66
>30	195	3.0	18	2.3	0.76	0.46–1.25	9	3.5	1.41	0.70–2.82	48	6.7	**1.89**	**1.29–2.75**
Binge drinking														
No drinking	4150	63.2	500	63.1		referent	137	53.9		referent	425	59.8		referent
Drinking, not binge	1609	24.5	196	24.7	0.89	0.74–1.07	74	29.1	**1.43**	**1.06–1.93**	134	18.9	**1.27**	**1.01–1.59**
Binge, ≥4/occasion	804	12.3	97	12.2	0.99	0.78–1.25	43	16.9	**1.71**	**1.19–2.45**	152	21.4	**1.53**	**1.21–1.92**
Drinking duration (months)														
0	4150	63.0	500	62.9		referent	137	54.2		referent	425	59.1		referent
1	1292	19.6	177	22.3	1.05	0.87–1.27	67	26.5	**1.64**	**1.20–2.22**	124	17.3	1.14	0.91–1.43
2	740	11.2	82	10.3	0.83	0.64–1.07	30	11.9	1.28	0.85–1.94	115	16.0	**1.86**	**1.45–2.40**
3	177	2.7	19	2.4	0.85	0.52–1.40	9	3.6	1.53	0.76–3.08	29	4.0	1.54	0.98–2.41
4	227	3.5	17	2.1	**0.55**	**0.33–0.91**	10	4.0	1.33	0.69–2.59	26	3.6	1.43	0.90–2.28
Drink type														
None	4150	63.0	500	63.0		referent	137	53.9		referent	425	59.3		referent
Spirits only[d]	428	6.5	51	6.4	1.05	0.77–1.43	20	7.9	1.45	0.89–2.37	78	10.9	**1.62**	**1.21–2.15**
Wine only	668	10.1	91	11.5	0.94	0.73–1.20	35	13.8	**1.60**	**1.08–2.39**	34	4.7	0.92	0.63–1.36
Beer only	510	7.7	58	7.3	0.92	0.68–1.23	26	10.2	**1.69**	**1.09–2.62**	81	11.3	**1.53**	**1.15–2.04**
> 1 type	832	12.6	94	11.8	0.84	0.66–1.07	36	14.2	1.34	0.91–1.98	99	13.8	**1.39**	**1.07–1.81**

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Following exclusion of those with or missing prepregnancy history of type 1 or type 2 diabetes, or missing/invalid valid alcohol data. Periconceptional was defined as 1 month prepregnancy through third month of pregnancy.

[b]Adjusted for race (Non-Hispanic white, Non-Hispanic black, Hispanic, other), age (12–19 years, 20–24 years, 25–29 years, 30–34 years, ≥35 years), and state of residence at time of infant's birth.

[c]Adjusted for race (Non-Hispanic white, Non-Hispanic black, Hispanic, other), age (12–17 years, 18–19 years, 20–24 years, 25–29 years, ≥30 years), state of residence at time of infant's birth, and periconceptional smoking (yes, no).

[d]Included mixed drinks and liquor shots.

Birth Defects Res A Clin Mol Teratol. Author manuscript; available in PMC 2018 July 12.