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Maternal alcohol use during pregnancy and associated morbidities in very low birthweight newborns

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Abstract

Background—We *hypothesized* that maternal alcohol use occurs in pregnancies that end prematurely and that *in utero* alcohol exposure is associated with an increased risk of morbidities of premature newborns.

Methods—In an observational study of mothers who delivered very low birth weight newborns 1500 grams (VLBW), maternal alcohol use was determined via a standardized administered questionnaire. We compared the effect of maternal drinking on the odds of developing late onset sepsis, bronchopulmonary dysplasia (BPD), Death, BPD or death (BPD/Death), days on oxygen or Any Morbidity (either late onset sepsis, BPD or Death). The effect of drinking amounts (light versus heavy) was also evaluated.

Results—One hundred twenty nine subjects who delivered 143 VLBW newborns were enrolled. Approximately one in three (34%) subjects reported drinking alcohol during the 1st Trimester ('Exposed'). Within the Exposed group, 15% reported drinking ≥ 7 drinks/week ('heavy') and 85% of the subjects reported drinking < 7 drinks/week ('light'). When controlling for maternal age, drug/tobacco use during pregnancy and neonatal gestational age, any drinking increased the odds of BPD/Death and Any Morbidity. Furthermore, light or heavy drinking increased the odds of BPD/Death and Any Morbidity, while heavy drinking increased the odds of late onset sepsis.

Conclusions—*In utero* alcohol exposure during the first trimester occurred in 34% of VLBW newborns. Maternal drinking in the first trimester was associated with significantly increased odds of neonatal morbidity. Further studies are warranted to determine the full effect of *in utero* alcohol exposure on adverse outcomes of VLBW premature newborns.

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Keywords

fetal alcohol; bronchopulmonary dysplasia; late onset sepsis; prematurity

INTRODUCTION

In utero alcohol exposure remains an important problem for the newborn, as was recently highlighted in a clinical report by the American Academy of Pediatrics.¹ As noted by the Academy, no amount of alcohol during pregnancy can be considered safe for the developing fetus. Although the Academy reports that maternal alcohol occurs in 8% of pregnancies,¹ other reports estimate alcohol exposure to be as high as 46% of all pregnancies.² Furthermore, *in utero* alcohol exposure has been associated with an increase in the risk of extreme prematurity (< 32 weeks of gestation).³ In a meta-analysis of maternal alcohol consumption, mothers who consumed more than 3 alcoholic drinks/day had a 23% increase in the risk of having a premature newborn.⁴

Our laboratory and others have demonstrated in experimental animal models that *in utero* ethanol deranges immune function, particularly in the neonatal lung.^{5–7} In clinical studies, we previously reported that alcohol exposure *in utero* was associated with an increased risk of neonatal infection in term newborns⁸ and sepsis in very low birth weight (VLBW) newborns.⁹ However, additional clinical data of alcohol's effects on the risk of sepsis and other measures of poor outcome in the premature newborn are lacking. Late onset sepsis (LOS) is critically important for VLBW newborns since it independently increases the risk of other significant morbidities such as bronchopulmonary dysplasia (BPD) or death.^{10, 11}

Fetal alcohol exposure is hallmarked by oxidative stress-induced injury to multiple developing organs.^{6, 7, 12–16} Due to the gestational immaturity of the antioxidant systems, the premature newborn is already at significant risk of increased oxidative stress and associated respiratory morbidities such as BPD.^{17, 18} Although a significant proportion of term newborns are noted to be exposed to alcohol *in utero*,^{19–21} they remain clinically under-identified at the time of birth²² and the clinical consequences of this exposure superimposed on prematurity remain undescribed.

Given this potential increased risk of premature delivery with maternal alcohol use during pregnancy superimposed on the risk of alcohol-induced oxidative stress to the premature infant, we *hypothesized* that 1) maternal alcohol use occurs in pregnancies that end prematurely and 2) that maternal alcohol use is associated with an increased odds of developing adverse morbidities of premature newborns. The primary objective of the current study was to define the prevalence of maternal alcohol use in VLBW premature newborns using our established administered maternal questionnaire.⁸ Our secondary objective was to determine whether maternal alcohol use during pregnancy is associated with an increase in the adverse morbidities of VLBW newborns particularly LOS, BPD, Death, or BPD/Death.

METHODS

Human participants

After approval from the Emory IRB (Emory IRB 00000976, Gauthier, PI), subjects were enrolled from Emory University Hospital Midtown and Grady Memorial Hospital in Atlanta, GA from May, 2009 through November 2013. Both Emory University Hospital Midtown and Grady Memorial Hospital have active delivery services in the city of Atlanta. Midtown services ~ 3,800 deliveries/ year and has a 36 bed Level III Neonatal Intensive Care Nursery. Grady Hospital has ~3,000 deliveries/year and is equipped with a ~60 bed Level III Neonatal Special Care nursery. Mothers of all VLBW neonates weighing < 1,500 grams who were admitted to the Newborn Intensive Care Units were eligible for enrollment into the study. Exclusion criteria included maternal refusal to participate.

Maternal Questionnaire/Interview

After written informed consent, the subjects underwent a structured personal interview with a trained research staff. The majority of interviews occurred in the first 48 hours after delivery, while the subjects remained hospitalized. During this interview, the research staff administered an extensive questionnaire to the subject. The questionnaire was modeled after those originally constructed by the Centers for Disease Control and Prevention and used in studies evaluating reported prenatal exposures such as alcohol,²³ including our previous study which evaluated the association between maternal alcohol exposure and infection of term newborns.⁸ During the interview, subjects were asked numerous questions about lifestyle and behaviors including alcohol consumption (beer, wine or liquor) before conception and during the pregnancy. Questions about alcohol consumption were asked for each of four time periods: the three months before conception, the first trimester (i.e., gestational ages 2 to 13 weeks), the second trimester (i.e., gestational ages 14 through 24 weeks), and the third trimester (i.e., gestational ages 25 weeks through delivery). A calendar was used to assist in maternal timing of alcohol consumption before and during pregnancy listing the dates of each trimester. Subjects were asked to report the frequency of alcohol consumption, the usual number of drinks consumed on days on which they drank, and the largest number of drinks consumed in a single day. Binge drinking was defined as consumption of at least five drinks in a single sitting. We then estimated the average number of drinks consumed each week (i.e. Frequency * Usual #). Newborns born to subjects who reported drinking alcohol during the 1st trimester of pregnancy were designated the 'Exposed' group while those born to subjects who denied alcohol use during the 1st trimester were designated the 'Non-exposed' group. Within the Exposed group, those who reported drinking ≥ 7 drinks/ week were defined as 'heavy drinking' and those who reported drinking < 7 drinks/week were defined as 'light drinking.'⁸

Subjects were also asked to report the following demographic information: race (White, African-American, or other), their highest grade of education (< high school, high school graduate, some college or technical school education, graduated from junior college, graduated from college, or obtained any Graduate education), their marital status (married, single, separated/divorced, or Other) and their yearly income (<\$25,000, \$25,001–\$55,000, \$55,001–\$70,000, or >\$70,000). Subjects were asked to report if they smoked tobacco before

or during pregnancy and if they used any illicit drugs (including marijuana, cocaine or ecstasy) before or during pregnancy. Each subject's medical record was reviewed by study staff for maternal medical and delivery room information. Subjects were identified with a study number and strict confidentiality was maintained.

Neonatal Outcomes

Neonatal morbidities were obtained from a thorough review of the medical record by the research staff. Adverse neonatal outcomes of interest included LOS (defined as positive blood culture after five days of life), BPD (defined as oxygen use at 36 weeks post-conceptional age), death, BPD or death (BPD/Death), days on supplemental oxygen, or a composite outcome (LOS, BPD or Death) defined as Any Morbidity. Other outcomes evaluated included intraventricular hemorrhage (IVH, grade 2 or higher), retinopathy of prematurity (ROP, grade 1 or higher) and necrotizing enterocolitis (NEC). Data were entered into a secure de-identified electronic data base (Emory Alcohol Lung Biology Center, Guidot PI) and then extracted for statistical analyses.

Statistical Analyses

Statistical analyses were performed using SPSS Version 21 (IBM, Armonk, NY) and SAS version 9.4 (Cary, NC, USA). Statistical significance was assessed at the 0.05 level. Descriptive statistics were calculated for all variables of interest and included: means and standard deviations, medians and interquartile ranges, and counts and percentages, when appropriate. Characteristics of subjects who reported alcohol use in the 1st Trimester and those who reported abstaining from alcohol were compared using Chi-square tests or two-sample t-tests. When expected cell counts were small (<5), a Fisher's exact test was used. Normality of continuous variables was assessed using histograms, normal probability plots and through the Anderson-Darling test for normality. For non-normal data, we compared the distribution of the continuous variable between the two groups using the Wilcoxon rank-sum or two-sample Kolmogorov-Smirnov test, as appropriate. Unadjusted and adjusted analyses were used to compare the odds of developing these morbidities in neonates exposed to any maternal drinking versus no exposure. For the adjusted models, the Hosmer-Lemeshow test was used to measure goodness of fit for our logistic models. Odds ratios and 95% confidence intervals were constructed using logistic regression models. Subgroup analyses compared those exposed to light drinking and those exposed to heavy drinking to those with no exposure. Odds ratios (OR) and associated 95% confidence intervals (CI) are presented. Since data regarding days on oxygen were non-normally distributed, these data were log transformed and analysis was carried out on the log-transformed data. Data were back transformed via exponentiation and presented as means with associated 95% confidence intervals.

RESULTS

Maternal Demographics

We enrolled 129 subjects who delivered 143 VLBW infants (7 sets of twins). The consent rate for enrollment in the study was 52%. Reasons for non-enrollment of subjects included maternal refusal to participate in the study (80%), subjects not approached due to early

neonatal death in the Newborn Intensive Care Unit before maternal consent for enrollment could be obtained (6%), maternal illness/inability to consent (5%), maternal incarceration (3%), and unknown (6%). The median age of consenting women was 25.5 years, 85% were African-American, and the majority of the subjects were unmarried. Maternal diagnosis of pregnancy induced hypertension (PIH) was noted in 15%, existing diabetes mellitus was noted in 6% of the subjects and gestational diabetes occurred in 27% (data not shown). The majority (90%) received prenatal care beginning at ~ 9 weeks of pregnancy, while only ~16% of the population reported they were trying to get pregnant with the current pregnancy (data not shown).

Based on maternal response during the interview, over 60% of the subjects reported drinking alcohol in the 3 months prior to pregnancy and approximately one third (38%; [95% CI: 27% – 43.4%]) of the subjects reported drinking alcohol in the 1st trimester. Only 10% of the subjects reported alcohol consumption during the 2nd trimester. The majority of those who drank in the 2nd Trimester (80%) also reported 1st Trimester drinking. No subject reported alcohol consumption in the 3rd trimester. Binge drinking was reported in 16.3% (95% CI: 10.7% – 23.4%) of the subjects prior to pregnancy and 6.6% of the subjects during the 1st trimester. Approximately 17% (95% CI: 11.4% – 24.5%) of the subjects smoked tobacco during pregnancy and 12% (95% CI: 7.1% – 18.6%) admitted to illicit drug use (including marijuana, cocaine or ecstasy).

Within the Exposed group, 15% of the subjects (7/45) reported heavy drinking and the remaining 85% of the subjects reported light drinking during the 1st trimester. Exposed subjects were significantly older than Non-exposed subjects ($p=0.012$). Tobacco smoking and illicit drug use during pregnancy were more than three-fold higher in Exposed compared to Non-exposed subjects ($p=0.001$ and $p=0.01$, respectively). There were no statistically significant differences in maternal race, gravidity, prenatal care, education, or income between Exposed and Non-exposed subjects (Table 1). There were no statistically significant differences in PIH, diabetes mellitus or gestational diabetes mellitus between Exposed and Non-exposed subjects (data not shown).

Neonatal Demographics

The neonatal population consisted of 143 VLBW newborns (49 Exposed and 94 Non-exposed) (Table 2). The mean birth weight of the cohort was 1064 grams and the mean gestational age of the newborns was 28.3 weeks. Exposed newborns were ~200 grams smaller ($p<0.001$) and were born ~ 1.5 weeks earlier than Non-exposed newborns ($p<0.001$). In a regression analyses we evaluated birth weight between the drinking groups (Exposed versus Non-exposed) while adjusting for gestational age. In this analyses, birth weight between the two groups were not significantly different (Non-exposed: 1085 grams, 95% CI (1045 – 1125) vs Exposed: 1024 grams, 95% CI (968 – 1081), $p=0.097$). There were no statistically significant differences in sex, Apgar scores, rate of C-Section, maternal steroid use, or premature prolonged rupture of membranes (PPROM) between the Exposed and Non-exposed newborns.

Analyses of the Association between any Maternal Drinking and Neonatal Morbidities

In this VLBW population, LOS occurred in 11% (95% CI: 6.5% – 17%) of the cohort, BPD occurred in 28% (95% CI: 19.9% – 37.1%), Death occurred in 4.6% (95% CI: 1.2%–8.0%), while 30% developed BPD/Death (95% CI: 22% – 39.4%). IVH occurred in 13% (95% CI: 7.4% – 18.9%), ROP in 13% (95% CI: 7.4%–19%) and NEC occurred in 9% (95% CI: 4% – 14%). In the univariate analysis comparing Exposed to Non-exposed, Exposure to alcohol was significantly associated with a higher odds of developing LOS (OR 4.53 [CI: 1.46–15.62], $p=0.009$), BPD (OR 2.54 [CI: 1.03–6.30], $p=0.042$), BPD/Death (OR 4.24 [CI: 1.75–10.53], $p=0.001$), or Any Morbidity (OR 4.18 [CI: 1.89–9.44], $p<0.001$) when compared to Non-exposed newborns (Table 3). Days on oxygen was prolonged approximately 1 week with any maternal drinking (Any drinking-22 days [95% CI: 15–33] vs None- 14 days [95% CI: 11–19]) but this approached but did not reach significance ($p=0.06$). After adjusting for maternal age, drug/tobacco use during pregnancy and gestational age (factors which significantly differed in Exposed versus Non-exposed), any alcohol exposure significantly increased the odds of BPD/Death (OR 4.06 [CI: 1.12–13.50], $p=0.022$) and Any Morbidity (OR 4.36 [CI: 1.50–12.63], $p=0.007$) (Table 3). Although the odds of ROP were significantly elevated with any alcohol exposure in the unadjusted analyses, there were no significant associations between any maternal drinking and increased risk of IVH, ROP or NEC after adjusting for maternal age, drug/tobacco use during pregnancy and gestational age (Supplemental Table 1). The Hosmer and Lemeshow Goodness-of Fit tests indicated adequate model fit for all multivariable models ($p > 0.77$ for all models).

Analyses of the Association between Maternal Drinking Amounts and Neonatal Morbidities

We then explored whether the level of alcohol exposure was associated with increased risks of neonatal morbidities. As noted, only 7 of the 45 subjects (~15%) who admitted to alcohol use in the 1st trimester reported drinking at levels ≥ 7 drinks/week ('Heavy') while the majority of subjects reported drinking at levels <7 drinks/week ('Light'). In the unadjusted analyses, light drinking was associated with increased odds of LOS (OR 3.57 [CI: 1.03–13.09], $p=0.045$), BPD (OR 2.72 [CI: 1.04–7.1], $p=0.041$), BPD/Death (OR 4.29 [CI: 1.68–11.2], $p=0.002$) and Any Morbidity (OR 3.87 [CI: 1.68–9.03], $p=0.001$) (Table 4). Days on oxygen was again prolonged approximately 1 week with any Light drinking (Light drinking-22 days [95% CI: 14–34] vs None- 14 days [95% CI: 11–19]) but this did not reach significance ($p=0.08$). Heavy drinking was associated with increased odds of LOS (OR 12.03 [CI: 1.82–75.95], $p=0.012$) or Any Morbidity (OR 6.48 [CI: 1.22–38.95], $p=0.029$) compared to no alcohol exposure (Table 4). After similarly adjusting for maternal age, drug/tobacco use during pregnancy and gestational age, the risk of BPD/Death with light drinking versus no exposure was significantly increased over 3 fold (OR 3.57 [CI 1.03–12.33], $p=0.044$), while the risk of Any Morbidity was significantly increased near 4 fold (OR 3.81 [CI 1.28–11.37], $p=0.017$). Furthermore, heavy drinking significantly increased the odds of LOS (OR 13.91 [CI 1.12–173.04], $p=0.041$), BPD/Death (OR 28.13 [CI 1.32–600.37], $p=0.033$) and Any Morbidity (OR 35.7 [CI 2.17–586.78], $p=0.012$). The Hosmer and Lemeshow Goodness-of Fit tests indicated adequate model fit for all multivariable models ($p > 0.53$ for all models).

DISCUSSION

In the current study, 34% of VLBW premature newborns were exposed to alcohol *in utero* and ~7% were exposed to binge drinking *in utero* per maternal report. Without the routine use of biological tests to clinically identify the alcohol-exposed pregnancy, structured maternal interviews and questionnaires have been used to investigate the association between maternal alcohol exposure and neonatal outcomes.⁸ Despite their intrinsic limitations in accurately identifying alcohol-exposed pregnancies,^{24, 25} maternal interviews are a practical approach to acquire such information, although they potentially under-report consumption and are most valid when administered antenatally.^{24, 26} Lester *et al* evaluated a VLBW newborn population and similarly reported that ~30% of the mothers reported alcohol use during pregnancy, but they did not comment on specific alcohol-related morbidities.²¹ In the National Birth Defects Prevention Study, which included the state of Georgia, 30% of women drank during their pregnancy while ~8.3% binge drank.²⁷ Our data from the current study is in agreement with this literature and suggests that at least one in three premature newborns in our newborn intensive care units is by maternal report alcohol-exposed. Drug use in the current study also fell within the range of that previously reported for VLBW populations. Lester *et al* noted maternal self-report of drug use at ~14%²¹ while a 2013 National Survey on Drug Use and Health noted illicit drug use during the 1st Trimester of pregnancy at 9%.²⁸ In the current study, maternal self-report of illicit drug use in the 1st trimester was 12%.

The current study is the first to specifically examine the association of alcohol exposure with morbidities of in VLBW premature newborns. Despite animal data suggesting that fetal alcohol exposure suppresses the immune response in the offspring,^{7, 16, 29, 30} clinical evidence specifically evaluating alcohol's effect on newborn immunity remains limited. Limited studies of children with fetal alcohol syndrome demonstrate increased rates of bacterial infections such as pneumonia.^{31, 32} In term newborns, we were the first to report that any alcohol exposure *in utero* carried a 2.5-fold increased risk of infection, while excessive maternal alcohol use (≥ 7 drinks/week) increased the risk of infection by 3–4-fold.⁸ The current study suggests that similar to our previous investigations in term newborns, the odds of developing LOS was significantly increased in VLBW premature newborns with exposure to heavy (≥ 7 drinks/week) drinking. LOS in VLBW infants is known to be associated with an increased risk of adverse outcomes such as BPD or death.³³

Multiple animal models suggest that *in utero* alcohol also alters the development of the lung,^{5, 6, 34–37} but no clinical data have been reported regarding pulmonary outcomes of alcohol-exposed newborns, particularly those born prematurely. In the current study population, we did not find a significance effect of alcohol exposure on the individual outcomes of BPD or neonatal Death. However, analyses adjusted for maternal age, drug/tobacco use during pregnancy and gestational age demonstrated that alcohol exposure increased the odds of the composite variable BPD/Death in the VLBW population. The composite outcome of BPD/Death is an important and commonly reported variable in clinical investigations of outcomes in this neonatal population.³⁸ These current data strongly suggest that additional clinical investigations with larger numbers evaluating alcohol's association with adverse pulmonary outcomes for the VLBW newborn are warranted.

This study has several limitations. Most notably, we were limited by a small sample size of 143 VLBW infants, with resultant small subgroups exposed to light or heavy maternal drinking. We were unable to evaluate the effects of alcohol longitudinally across pregnancy due to low sample size and the fact that reported maternal alcohol use declined across gestation. Due to this small sample, our adjusted analyses were limited to the covariates of maternal age, drug/tobacco use during pregnancy and gestational age. We chose to adjust for these maternal factors since they were significantly different in the Exposed group versus the Non-exposed. We also adjusted for gestational age since it was significantly lower in the Exposed group and most strongly confounds most morbidities of prematurity. Thus, given our low sample size and resultant wide confidence intervals, particularly in the subgroup analyses, our findings demonstrating alcohol-associated increased odds of these neonatal morbidities should be interpreted with caution, but nevertheless warrant additional investigations.

Although we report similar prevalence of LOS and BPD in VLBW infants to that described in the literature,^{11, 39} the findings from our cohort may also not be generalizable to other Neonatal Intensive Care Unit (NICU) populations. The majority of our cohort were African-American as is reflective of our nursery population. Our identification of alcohol exposure relied on maternal disclosure of alcohol use during pregnancy via a standardized personal interview after delivery. We recognize that the survey instrument used carries inherent risks of underestimating alcohol ingestion as well as inherent risks of multiple types of bias, including cognitive biases and memory bias. Furthermore, with our 52% consent rate we cannot exclude potential selection bias in the study population. Despite the inherent limitations of our maternal survey, we believe that there are no compelling reasons to suspect that subjects overestimated or exaggerated their alcohol intake in this survey. Although retrospective report of alcohol use via maternal interview has been described as superior to concurrent reporting,²⁴ we, as have others, postulate that the detection rates of alcohol exposure reported in this study may be an under-representation of the true prevalence of alcohol use during pregnancy.^{24, 25, 40}

In summary, this study supports the hypothesis that *in utero* alcohol exposure occurs in VLBW premature newborns admitted to the newborn intensive care unit. Furthermore, *in utero* alcohol exposure is associated with an alarming increased odds of developing adverse morbidities often seen in premature newborns, most notably LOS and BPD/Death. These data justify the import need for additional multicenter investigations aimed to formally identify the alcohol-exposed VLBW newborn and confirm in a larger cohort alcohol's association with neonatal morbidities of premature newborns.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

VLBW	very low birthweight
LOS	Late onset sepsis
BPD	Bronchopulmonary dysplasia
OR	Odds ratios
CI	Confidence intervals

References

- Williams JF, Smith VC, Committee On Substance A. Fetal Alcohol Spectrum Disorders. *Pediatrics*. 2015; 136:e1395–e1406. [PubMed: 26482673]
- McDonald SW, Hicks M, Rasmussen C, et al. Characteristics of women who consume alcohol before and after pregnancy recognition in a Canadian sample: a prospective cohort study. *Alcohol Clin Exp Res*. 2014; 38:3008–3016. [PubMed: 25581655]
- Sokol RJ, Janisse JJ, Louis JM, et al. Extreme prematurity: an alcohol-related birth effect. *Alcohol Clin Exp Res*. 2007; 31:1031–1037. [PubMed: 17403063]
- Patra J, Bakker R, Irving H, et al. Dose-response relationship between alcohol consumption before and during pregnancy and the risks of low birthweight, preterm birth and small for gestational age (SGA)-a systematic review and meta-analyses. *Bjog*. 2011; 118:1411–14121. [PubMed: 21729235]
- Lazic T, Wyatt TA, Matic M, et al. Maternal alcohol ingestion reduces surfactant protein A expression by preterm fetal lung epithelia. *Alcohol*. 2007; 41:347–355. [PubMed: 17889311]
- Sozo F, O'Day L, Maritz G, et al. Repeated ethanol exposure during late gestation alters the maturation and innate immune status of the ovine fetal lung. *Am J Physiol Lung Cell Mol Physiol*. 2009; 296:L510–L518. [PubMed: 19112099]
- Gauthier TW, Ping XD, Harris FL, et al. Fetal alcohol exposure impairs alveolar macrophage function via decreased glutathione availability. *Pediatr Res*. 2005; 57:76–81. [PubMed: 15531743]
- Gauthier TW, Drews-Botsch C, Falek A, et al. Maternal alcohol abuse and neonatal infection. *Alcohol Clin Exp Res*. 2005; 29:1035–1043. [PubMed: 15976530]
- Gauthier TW, Manar MH, Brown LAS. Is maternal alcohol use a risk factor for early-onset sepsis in the premature newborn? *Alcohol*. 2004; 33:139–145. [PubMed: 15528011]
- Shah J, Jefferies AL, Yoon EW, et al. Risk Factors and Outcomes of Late-Onset Bacterial Sepsis in Preterm Neonates Born at < 32 Weeks' Gestation. *Am J Perinatol*. 2014
- Hornik CP, Fort P, Clark RH, et al. Early and late onset sepsis in very-low-birth-weight infants from a large group of neonatal intensive care units. *Early Hum Dev*. 2012; 88(Suppl 2):S69–S74. [PubMed: 22633519]
- Gundogan F, Elwood G, Mark P, et al. Ethanol-Induced Oxidative Stress and Mitochondrial Dysfunction in Rat Placenta: Relevance to Pregnancy Loss. *Alcohol Clin Exp Res*. 2009
- Ojeda ML, Nogales F, Jotty K, et al. Dietary selenium plus folic acid as an antioxidant therapy for ethanol-exposed pups. *Birth Defects Res B Dev Reprod Toxicol*. 2009; 86:490–495. [PubMed: 19918952]
- Coyle P, Martin SA, Carey LC, et al. Ethanol-mediated fetal dysmorphology and its relationship to the ontogeny of maternal liver metallothionein. *Alcohol Clin Exp Res*. 2009; 33:1051–1058. [PubMed: 19302082]

15. Dong J, Sulik KK, Chen SY. Nrf2-mediated transcriptional induction of antioxidant response in mouse embryos exposed to ethanol in vivo: implications for the prevention of fetal alcohol spectrum disorders. *Antioxid Redox Signal*. 2008; 10:2023–2033. [PubMed: 18759561]
16. Gauthier TW, Young PA, Gabelaia L, et al. In utero ethanol exposure impairs defenses against experimental group B streptococcus in the term Guinea pig lung. *Alcohol Clin Exp Res*. 2009; 33:300–306. [PubMed: 19032578]
17. Davis JM, Auten RL. Maturation of the antioxidant system and the effects on preterm birth. *Semin Fetal Neonatal Med*. 2010; 15:191–195. [PubMed: 20452845]
18. Buczynski BW, Maduekwe ET, O'Reilly MA. The role of hyperoxia in the pathogenesis of experimental BPD. *Semin Perinatol*. 2013; 37:69–78. [PubMed: 23582960]
19. Albertsen K, Andersen AM, Olsen J, et al. Alcohol consumption during pregnancy and the risk of preterm delivery. *Am J Epidemiol*. 2004; 159:155–161. [PubMed: 14718217]
20. Ebrahim SH, Gfroerer J. Pregnancy-related substance use in the United States during 1996–1998. *Obstet Gynecol*. 2003; 101:374–379. [PubMed: 12576263]
21. Lester BM, ElSohly M, Wright LL, et al. The Maternal Lifestyle Study: drug use by meconium toxicology and maternal self-report. *Pediatrics*. 2001; 107:309–317. [PubMed: 11158464]
22. Mattson SN, Riley EP, Gramling L, et al. Heavy prenatal alcohol exposure with or without physical features of fetal alcohol syndrome leads to IQ deficits. *J Pediatr*. 1997; 131:718–721. [PubMed: 9403652]
23. Drews CD, Murphy CC, Yeargin-Allsopp M, et al. The relationship between idiopathic mental retardation and maternal smoking during pregnancy. *Pediatrics*. 1996; 97:547–553. [PubMed: 8632944]
24. Alvik A, Haldorsen T, Groholt B, et al. Alcohol consumption before and during pregnancy comparing concurrent and retrospective reports. *Alcohol Clin Exp Res*. 2006; 30:510–515. [PubMed: 16499492]
25. Lange S, Shield K, Koren G, et al. A comparison of the prevalence of prenatal alcohol exposure obtained via maternal self-reports versus meconium testing: a systematic literature review and meta-analysis. *BMC Pregnancy Childbirth*. 2014; 14:127. [PubMed: 24708684]
26. Jacobson SW, Chiodo LM, Sokol RJ, et al. Validity of maternal report of prenatal alcohol, cocaine, and smoking in relation to neurobehavioral outcome. *Pediatrics*. 2002; 109:815–825. [PubMed: 11986441]
27. Ethen MK, Ramadhani TA, Scheuerle AE, et al. Alcohol consumption by women before and during pregnancy. *Matern Child Health J*. 2009; 13:274–285. [PubMed: 18317893]
28. Administration SAaMHS. Results from the 2013 National Survey on Drug Use and Health: Summary of National NSDUH Series H-48. 2014 HHS Publication No (SMA) 14-4863 <http://www.drugwarfacts.org/cms/Pregnancy#sthash.d9gtV4v8.uOpYn00w.dpuf>:26.
29. Gauthier TW, Ping XD, Gabelaia L, et al. Delayed neonatal lung macrophage differentiation in a mouse model of in utero ethanol exposure. *Am J Physiol Lung Cell Mol Physiol*. 2010; 299:L8–L16. [PubMed: 20382747]
30. Ping XD, Harris FL, Brown LA, et al. In vivo dysfunction of the term alveolar macrophage after in utero ethanol exposure. *Alcohol Clin Exp Res*. 2007; 31:308–316. [PubMed: 17250624]
31. Johnson S, Knight R, Marmer DJ, et al. Immune deficiency in fetal alcohol syndrome. *Pediatr Res*. 1981; 15:908–911. [PubMed: 7195540]
32. Kvigne VL, Leonardson GR, Borzelleca J, et al. Hospitalizations of children who have fetal alcohol syndrome or incomplete fetal alcohol syndrome. *S D Med*. 2009; 62:97, 9, 101–103. [PubMed: 19480273]
33. Stoll BJ, Hansen N, Fanaroff AA, et al. Changes in pathogens causing early-onset sepsis in very-low-birth-weight infants. *N Engl J Med*. 2002; 347:240–247. [PubMed: 12140299]
34. Wang X, Gomutputra P, Wolgemuth DJ, et al. Effects of acute alcohol intoxication in the second trimester of pregnancy on development of the murine fetal lung. *Am J Obstet Gynecol*. 2007; 197:269 e1–269 e4. [PubMed: 17826415]
35. Lazic T, Sow FB, Van Geelen A, et al. Exposure to ethanol during the last trimester of pregnancy alters the maturation and immunity of the fetal lung. *Alcohol*. 2011; 45:673–680. [PubMed: 21163613]

36. Sozo F, Vela M, Stokes V, et al. Effects of prenatal ethanol exposure on the lungs of postnatal lambs. *Am J Physiol Lung Cell Mol Physiol*. 2011; 300:L139–L147. [PubMed: 21036920]
37. Zelner I, Kenna K, Brien JF, et al. Meconium fatty acid ethyl esters as biomarkers of late gestational ethanol exposure and indicator of ethanol-induced multi-organ injury in fetal sheep. *PLoS ONE*. 2013; 8:e59168. [PubMed: 23533604]
38. Bassler D, Plavka R, Shinwell ES, et al. Early Inhaled Budesonide for the Prevention of Bronchopulmonary Dysplasia. *N Engl J Med*. 2015; 373:1497–1506. [PubMed: 26465983]
39. Lapcharoensap W, Gage SC, Kan P, et al. Hospital variation and risk factors for bronchopulmonary dysplasia in a population-based cohort. *JAMA Pediatr*. 2015; 169:e143676. [PubMed: 25642906]
40. Ernhart CB, Morrow-Tlucak M, Sokol RJ, et al. Underreporting of alcohol use in pregnancy. *Alcohol Clin Exp Res*. 1988; 12:506–511. [PubMed: 3056071]

Table 1

Maternal demographics of the overall study population and of the alcohol Exposed and Non-exposed subgroups.

CHARACTERISTIC	Overall (N = 129)	Exposed (N = 45)	Non-exposed (N = 84)
Maternal Age (n = 116)			
Years, median (25 th –75 th)	25.5 (22.4–32.9)	30.7 (22.6–34.6) *	24.9 (22.4–30.9)
Race, N (%) (n = 129)			
White	9 (7.0)	5 (11.1)	4 (4.8)
African-American	110 (85.3)	39 (86.7)	71 (84.5)
Other	8 (6.2)	1 (2.2)	7 (8.3)
Unknown	2 (1.6)	0 (0.0)	2 (2.4)
Gravidity, median (25th–75th) (n = 126)			
Total	2 (1–4)	2 (1–4)	2 (1–4)
Livebirth	2 (1–3)	2 (1–2)	2 (1–3)
Losses	0 (0–1)	0 (0–2)	0 (0–1)
Received Prenatal Care (n = 129)			
Yes, N (%)	115 (89.2)	43 (95.6)	72 (85.7)
Education, N (%) (n = 127)			
< High school	21 (16.5)	7 (15.6)	14 (17.1)
High school graduate	49 (38.6)	14 (31.1)	35 (42.7)
Some college/technical school	32 (25.2)	13 (28.9)	19 (23.2)
Junior college graduate	5 (3.9)	0 (0.0)	5 (6.1)
College graduate	13 (10.2)	7 (15.6)	6 (7.3)
Any Graduate education	7 (5.5)	4 (8.9)	3 (3.7)
Income/year, N (%) (n = 128)			
< \$25,000	60 (46.9)	20 (45.5)	40 (47.6)
\$25,001 – \$55,000	29 (22.7)	10 (22.7)	19 (22.6)
\$55,001 – \$70,000	5 (3.9)	0 (0.0)	5 (3.9)
> \$70,000	12 (9.4)	7 (15.9)	5 (6.0)
Marital Status, N (%) (n = 127)			
Married	24 (18.9)	7 (15.6)	17 (20.7)
Single	99 (78.0)	37 (82.2)	62 (75.6)
Separated/Divorced	3 (2.4)	1 (2.2)	2 (2.4)
Other	1 (0.8)	0 (0.0)	1 (1.2)
Tobacco Smoking, N (%) (n = 128)			
Before pregnancy	27 (21.1)	15 (33.3) *	12 (14.5)
During pregnancy	22 (17.1)	14 (31.1) **	8 (9.5)

CHARACTERISTIC	Overall (N = 129)	Exposed (N = 45)	Non-exposed (N = 84)
Illicit Drug Use, N (%) (n = 125)			
Before pregnancy	23 (18.4)	12 (26.1)	11 (13.9)
During pregnancy	15 (12.0)	10 (23.4) **	5 (6.1)

* p = 0.05 Exposed versus Non-exposed,

** p = 0.01 Exposed versus Non-exposed

Table 2

Neonatal demographics of the overall study population and of the alcohol Exposed and Non-exposed subgroups.

CHARACTERISTIC	Overall (N = 143)	Exposed (N = 49)	Non-exposed (N = 94)
Birth Weight, grams (n = 142)			
Mean ± SD	1,064.0 ± 263.1	941.4 ± 293.0 ***	1,128.6 ± 221.4
Gestational Age, weeks (n = 142)			
Mean ± SD	28.3 ± 2.3	27.2 ± 2.4 ***	28.9 ± 2.1
Sex, Male (n = 142)			
N (%)	75 (52.8)	29 (59.2)	46 (49.5)
Apgar Score			
% 7			
1 minute (n = 140)	81	29	52
5 minutes (n = 139)	45	17	29
10 minutes (n = 56)	43	20	23
Delivery Route (n = 142)			
C-Section, N (%)	103 (72.5)	35 (72.9)	68 (72.3)
Maternal Steroid Use (n = 143)			
Yes, N (%)	46 (32.2)	19 (38.8)	27 (28.7)
PPROM (n = 142)			
Yes, N (%)	36 (25.2)	18 (35.3)	18 (20.9)

p = 0.001 Exposed versus Non-exposed

Table 3

Association between Any Maternal Drinking and Neonatal Morbidities

Morbidity	Unadjusted		Adjusted [#]	
	Any Drinking vs. None		Any Drinking vs. None	
	OR (95% CI)	p value	OR (95% CI)	p value
LOS	4.53 (1.46 – 15.62)	0.009	2.83 (0.66–12.16)	0.162
BPD	2.54 (1.03–6.30)	0.042	2.13 (0.68–6.67)	0.196
Death	5.16 (0.98 – 39.71)	0.053	3.28 (0.33 – 87.39)	0.341
BPD/Death	4.24 (1.75 – 10.53)	0.001	4.06 (1.12–13.50)	0.022
Any Morbidity[^]	4.18 (1.89 – 9.44)	< 0.001	4.36 (1.50 – 12.63)	0.007

[#] Adjusted for maternal age, drug/tobacco use during pregnancy and gestational age[^] Composite outcome which includes either LOS, BPD or Death

Table 4

Association between Maternal Drinking Amounts⁺ and Neonatal Morbidities⁺ Drinking amounts: Light (< 7 drinks/week); Heavy (≥ 7 drinks/week)

	Unadjusted			
Morbidity	Light Drinking vs. None		Heavy Drinking vs. None	
	OR (95% CI)	p value	OR (95% CI)	p value
LOS	3.57 (1.03 – 13.09)	0.045	12.03 (1.82 – 75.95)	0.012
BPD	2.72 (1.04–7.1)	0.041	1.82 (0.22–11.26)	0.526
Death	4.78 (0.65 – 54.9)	0.146	7.34 (0.11 – 161.05)	0.391
BPD/Death	4.29 (1.68 – 11.2)	0.002	3.98 (0.62 – 25.41)	0.137
Any Morbidity [^]	3.87 (1.68 – 9.03)	0.001	6.48 (1.22 – 38.95)	0.029
	Adjusted [#]			
Morbidity	Light Drinking vs. None		Heavy Drinking vs. None	
	OR (95% CI)	p value	OR (95% CI)	p value
LOS	2.23 (0.48–10.31)	0.309	13.91 (1.12–173.04)	0.041
BPD	2.01 (0.62–6.52)	0.244	3.30 (0.32–33.88)	0.315
Death	2.14 (0.22 – 20.49)	0.510	13.44 (0.48 – 372.84)	0.125
BPD/Death	3.57 (1.03–12.33)	0.044	28.13 (1.32–600.37)	0.033
Any Morbidity [^]	3.81 (1.28 – 11.37)	0.017	35.70 (2.17 – 586.78)	0.012

[#] Adjusted for maternal age, drug/tobacco use during pregnancy and gestational age

[^] Composite outcome which includes either LOS, BPD or Death