CLINICAL INVESTIGATION

Maternal Alcohol Use During Pregnancy and Associated Morbidities in Very Low Birth Weight 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 (VLBW) ≤1,500 g, 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 (LOS), bronchopulmonary dysplasia (BPD), death, BPD or Death days on oxygen or any morbidity (either LOS, BPD or death). The effect of drinking amounts (light versus heavy) was also evaluated.

Results: A total of 129 subjects who delivered 143 VLBW newborns were enrolled. Approximately 1 in 3 (34%) subjects reported drinking alcohol during the first 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 or tobacco use during pregnancy and neonatal gestational age, any drinking increased the odds of BPD or Death and any morbidity. Furthermore, light or heavy drinking increased the odds of BPD or Death and any morbidity, whereas heavy drinking increased the odds of LOS.

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 the adverse outcomes of VLBW premature newborns.

Key Indexing Terms: Fetal alcohol; Bronchopulmonary dysplasia; Late-onset sepsis; Prematurity. **[Am J Med Sci 2016;▮(▮):▮▮▮–▮▮▮.]**

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 per 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 newborns [8] 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 as 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] Owing 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 underidentified at the time of birth[22] 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 or Death.

METHODS

Human Participants

After approval from the Emory Institutional Review Board (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 g 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 and Interview

After written informed consent, the subjects underwent a structured personal interview with a trained research staff member. Most interviews occurred in the first 48 hours after delivery, whereas 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 that 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 pregnancy. Questions about alcohol consumption were asked for each of 4 periods—the 3 months before conception, the first trimester (i.e., gestational ages 2-13 weeks); the second trimester (i.e., gestational ages 14-24 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 5 drinks in a single sitting. We then estimated the average number of drinks consumed each week (i.e., frequency X usual #). Newborns born to subjects who reported drinking alcohol during the first trimester of pregnancy were designated the "exposed" group, whereas those born to subjects who denied alcohol use during the first trimester were designated the "nonexposed" 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 (less than 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 or 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 5 days of life), BPD (defined as oxygen use at 36 weeks post–conceptional age), death, BPD or death (BPD or 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 deidentified 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). 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 first 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