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REGULAR ARTICLE

Alcohol during pregnancy worsens acute respiratory infections in children

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ABSTRACT

Aim: This study explored whether alcohol consumption during pregnancy increased the risk of life-threatening respiratory infections in children.

Methods: We prospectively evaluated children under the age of two years admitted to hospitals in Buenos Aires, Argentina, with severe acute respiratory infections during the winters of 2011 and 2012. Information on maternal alcohol consumption during the third trimester of pregnancy was collected using standardised questionnaires and categorised as never, low if it was once a week and high if it was equal or more than once a week.

Results: Of the 3423 children hospitalised with acute respiratory infection, 2089 (63.7%) had respiratory syncytial virus (RSV). Alcohol consumption during the last trimester was reported by 398 mothers (12.4%) and categorised as low (n = 210, 6.5%) or high (n = 188, 5.9%). A greater effect on life-threatening respiratory infection, defined as oxygen saturation of or up to 87%, was observed with higher alcohol intake due to all viruses and specifically RSV in the logistic regression analyses. Alcohol consumption was strongly associated with life-threatening disease, particularly in boys whose adjusted odds ratio rose from 3.67 to 13.52 when their mothers drank alcohol.

Conclusion: Alcohol consumption during pregnancy was associated with life-threatening respiratory infections in boys.

BACKGROUND

Alcohol consumption during pregnancy is a major public health concern because of the potential long-term physical, neurodevelopmental, endocrine and behavioural adverse consequences for children (1,2). Prenatal exposure to high levels of alcohol can result in many harmful effects in the developing foetus, including foetal alcohol syndrome and foetal alcohol spectrum disorders, which are characterised by growth retardation, brain dysmorphology and dysfunction and craniofacial anomalies (3,4).

There are conflicting reports as to whether very low levels of alcohol consumption during pregnancy are also associated with severe outcomes in exposed children (1,5). Limited evidence suggests that *in utero* alcohol exposure results in an increased incidence of minor and life-threatening bacterial infections and can decrease white blood cell counts in cord blood (6). Furthermore, limited alcohol consumption during gestation appears to increase a newborn infant's risk for infections (7). Perhaps some of the best evidence to date about the harmful effects of low alcohol intake during pregnancy comes from neurodevelopmental assessments, where very low levels of alcohol consumption had negative, persistent consequences on mental health outcomes (8). In fact, the current literature suggests that some of these effects may be influenced by gender. For example, mental health problems exhibited a gender-specific interaction with alcohol, but were only detected in girls (8). Conversely, the hypothalamic-pituitary-adrenal axis response to prenatal alcohol exposure showed greater cortisol levels in exposed boys (9).

Abbreviations
ARI, Acute respiratory infections; LRTI, Lower respiratory tract infection; OR, Odds ratio; RSV, Respiratory syncytial virus; RT-PCR, Real-time reverse transcriptase polymerase chain reaction; SPO2, Oxygen saturation.

Key notes

- This study explored whether alcohol consumption during the last trimester of pregnancy increased the risk of life-threatening respiratory infections in 3423 children hospitalised under the age of two years.
- One in eight of the mothers used alcohol during the last trimester, and it was high in just under 6% of this Argentinian population.
- We found that alcohol consumption during pregnancy was associated with life-threatening respiratory infections in boys.

Little is known about the effects of prenatal alcohol exposure on the developing lungs (10,11). Although alcohol consumption during pregnancy increases the risk of low birthweight due to both premature birth and intrauterine growth retardation (12), the consequences of maternal alcohol consumption on the severity of respiratory infections in children are unknown. Animal models have demonstrated that prenatal ethanol exposure alters extracellular matrix deposition, pro-inflammatory cytokine production and surfactant gene expression in the lungs (10,13,14). Therefore, significant long-term pulmonary effects may ensue from foetal alcohol exposure.

Acute respiratory infections (ARI) are the main paediatric cause of hospitalisation in infants and young children worldwide. The respiratory syncytial virus (RSV) is the most frequent agent of severe ARI (15,16), with an estimated 2.8–4.3 million children hospitalised every year (16). Most of these episodes resolve without major complications, but children with severe hypoxaemia face an increased risk of death (17). Identifying risk factors for life-threatening disease is important for targeted primary preventive interventions.

Interestingly, even though young infants with ARI have spent more time inside their mother's womb than in the outside world, risk factors for severe disease mainly focus on exposures occurring from the time of birth until infection (18,19). Attention to prenatal exposures has been limited (15,20).

The aim of this study was to explore whether alcohol consumption during pregnancy increased the risk of life-threatening ARI. We did this by conducting a prospective evaluation of hospitalised infants and children younger than two years of age in Buenos Aires, Argentina, during the winters of 2011 and 2012.

METHODS

Population and study period

During the winter respiratory seasons of 2011 and 2012, we conducted a multicentre prospective hospital-based study in a catchment population of 56 560 children younger than two years of age who received care from 12 public hospitals in the Southern Region of Buenos Aires, Argentina (15,21,22). Severe ARI was defined as the sudden onset of cough, wheezing, retractions and, or, crackles, with or without fever, and an oxygen saturation (SPO2) <93% at rest when breathing room air (15). Infants and young children were considered to have life-threatening disease when they presented with an SPO2 ≤87% on admission. We selected oxygen saturation as the endpoint for life-threatening disease, as in our previous study (15), because there were variations between the units. Some did not have intensive care facilities, some had limited access to equipment for mechanical ventilation, and in some cases, hospital admission times may have been affected by social factors.

The study was approved by the institutional review boards at the participating institutions, the state of Buenos Aires and Vanderbilt University. Informed consent was obtained from all the parents or guardians.

Epidemiological data

Data were collected using questionnaires specifically designed for the study (15). Information about potential confounders for severe disease included breastfeeding status, gender, age, structural poverty, an adolescent mother of <18 years old, maternal asthma diagnosed by a physician, prematurity of <37 weeks of gestation at birth and underlying chronic illnesses due to immunodeficiency, congenital heart disease or neurological disorder. The confounders also included malnutrition, defined as the percentage of the infant's weight compared to that of a normal child of the same age according to the World Health Organization (WHO) and categorised as mild (75–90%) or moderate to severe (<75%) (15,17,18). Structural poverty was evaluated by collecting data on the house, including whether it was made of a precarious mixture of mud and tin, whether it had a dirt floor and the sewage arrangements. Household income was defined as low when the monthly income was less than US $200, crowding was defined as three or more people per room and the poverty criteria also included malnutrition and smoking at home. The maternal diet during pregnancy was assessed as previously described (15). We previously reported that excessive carbohydrate ingestion and low intake of fruits and vegetables during pregnancy was associated with life-threatening ARI in infants and young children enrolled during 2011 in this same region (15). These earlier findings were aligned with our hypothesis that dietary habits during pregnancy would be shown to modulate the risk for severe infant lower respiratory tract infection (LRTI). All enrolled children were monitored daily during hospitalisation using specifically designed forms until discharge (15).

Data on maternal alcohol consumption during the third trimester of pregnancy were obtained using a standardised questionnaire while the infants and children were hospitalised with ARI. Mothers were asked about how often they had drunk alcohol in the 90 days before delivery. Given that we did not expect significant changes in dietary habits between early and late pregnancy (23), the reference period was limited to the last trimester of pregnancy. The possible responses to alcohol intake were never, a low level of less than once a week and a high level of one or more times a week (2,24). As the referenced timeframe for detailed recall was 90 days before delivery, information on the number of drinks per intake was not obtained.

Children were considered to have life-threatening disease if they presented with an SPO2 equal or <87% on admission, as previously described (15,17).

Viral diagnosis

Nasopharyngeal aspirates were obtained from all eligible subjects at the time of hospital admission and were evaluated in duplicates by real-time reverse transcriptase polymerase chain reaction (RT-PCR) for RSV and other

respiratory viruses, including human rhinoviruses (HRV) and influenza A viruses (15).

Statistical analysis

Chi-square, analysis of variance (ANOVA) and Student's *t*-test were used to compare the characteristics of children where appropriate. *Post hoc* analysis was performed using the Bonferroni test. Epidemiological and clinical factors considered in the analysis included variables from three major categories. The socio-economic category comprised a precariously built house, dirt floor, no sewage facilities at home, smoking at home, malnutrition, crowding, an adolescent mother, household income and parental education. The pregnancy category comprised smoking during pregnancy, antibiotics during pregnancy, carbohydrate intake, fruits and vegetable intake and maternal asthma. The infant category comprised age, sex, birthweight, prematurity, intrauterine growth retardation, breastfeeding and underlying chronic illness.

Stepwise multivariable logistic regression was performed on risk factors that were associated with an adverse outcome at $p \leq 0.20$ in the univariable analysis. A p value of <0.05 was considered significant.

An interaction term was generated with gender and alcohol consumption in the logistic regression model to establish gender-specific effects of alcohol intake during pregnancy on paediatric lung infections. All statistical analyses were performed using Stata 11.2.

RESULTS

Study population

During 2011 and 2012, 3423 children hospitalised with severe ARI were prospectively identified. RSV was detected in 2089 (63.7%) of the patients, the human rhinovirus (HRV) in 22% and Influenza A viruses in 3.1%. The majority of children admitted with ARI (62.0%), and specifically with RSV (63.6%), were younger than six months.

Alcohol consumption during the last trimester of pregnancy was reported by 398 (12.4%) mothers, and the levels were categorised as low (n = 210, 6.5%) and high (n = 188, 5.9%). Beer was the favourite alcoholic beverage in our study population, with 103 women, 7.1% of the total cohort, reporting low consumption and 56 (3.8%) reporting high consumption, followed 42 (3.0%) reporting low consumption of red wine and 26 (1.9%) reporting high consumption.

Mothers who admitting to alcohol intake during the third trimester of pregnancy were more likely to live in crowded homes, have a lower income, have smoked during pregnancy and have eaten a prenatal diet that was comparatively devoid of fruits and vegetables and rich in refined carbohydrates. Detailed comparisons between the groups are presented in Table S1.

Among patients hospitalised with ARI, exposure to alcohol during pregnancy exhibited a strong association with life-threatening disease, with an SPO2 of or up to 87%, in univariable and multivariable logistic regression analyses (Table 1). Univariable analysis of all the selected outcomes is shown in TS2.

A similar deleterious effect from alcohol intake was observed in children infected with RSV (Table 1). In line with our evaluation of the 2011 population, logistic regression showed that a high carbohydrate intake during the last trimester of pregnancy was associated with an increased risk for life-threatening disease, with an odds ratio (OR) of 2.98 and a 95% confidence interval (95%CI) of 2.11–8.83. Chronic illnesses in infancy (OR = 2.67, 95%CI, 1.19–5.98) were also associated with an increased risk, but breastfeeding was protective (OR = 0.38, 95%CI, 0.22–0.67).

Alcohol consumption was strongly associated with life-threatening disease in hospitalised boys, an observation confirmed by logistic regression, but interestingly, this was no observed for girls (Figs 1 and 2). In fact, an interaction between gender and alcohol consumption during pregnancy was found to affect the severity of ARI (p = 0.03).

Table 1 Alcohol consumption during pregnancy and the risk of life-threatening ARI and RSV infection

	SPO2 ≤ 87% (n, %)	SPO2 >87% (n, %)	Crude OR		Adjusted‡ OR	
			OR	95% CI	OR	95% CI
a. Life-threatening ARI						
No alcohol consumption	195 (75.9)	2010 (88.6)	REF		REF	
Low alcohol consumption*	26 (10.1)	135 (6)	1.99	1.27–3.1	2.97	1.27–6.92
High alcohol consumption†	36 (14)	123 (5.4)	3.01	2.02–4.5	4.13	2.11–8.83
b. Life-threatening RSV infection						
No alcohol consumption	130 (74.7)	1270 (88)	REF		REF	
Low alcohol consumption*	18 (10.3)	89 (6.2)	2.62	1.26–5.45	3.04	1.06–8.71
High alcohol consumption†	26 (15)	84 (5.8)	3.12	1.94–5.02	5.38	2.2–13.21

*Low alcohol consumption: <1 time per week; †High alcohol consumption: ≥1 times a week. ‡Adjusted for socio-economic variables (precarious house made of tin/mud, dirt floor, no sewage, smoking at home, malnutrition, crowding, adolescent mother, household income), pregnancy variables (smoking during pregnancy, antibiotics during pregnancy, carbohydrates intake, fruits and vegetables intake, maternal asthma) and infant variables (age, sex, birthweight, prematurity, intrauterine growth retardation, breastfeeding, underlying chronic illness). Stepwise multivariable logistic regression was performed for risk factors associated with adverse outcomes at a $p \leq 0.20$.

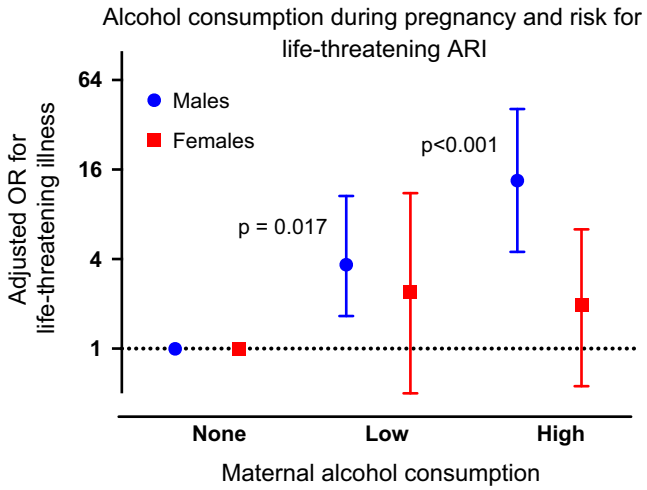

Figure 1 Maternal alcohol consumption during the third trimester of pregnancy is associated with increased odds for life-threatening ARI: crude OR, low alcohol dose 2.31 (95% CI, 1.26–4.26) and high alcohol dose 4.14 (95% CI, 2.46–6.97); adjusted OR, low alcohol dose 3.67 (95% CI, 1.26–10.66) and high alcohol dose 13.52 (95% CI, 4.47–40.82) vs nonconsumption group in hospitalised boys.

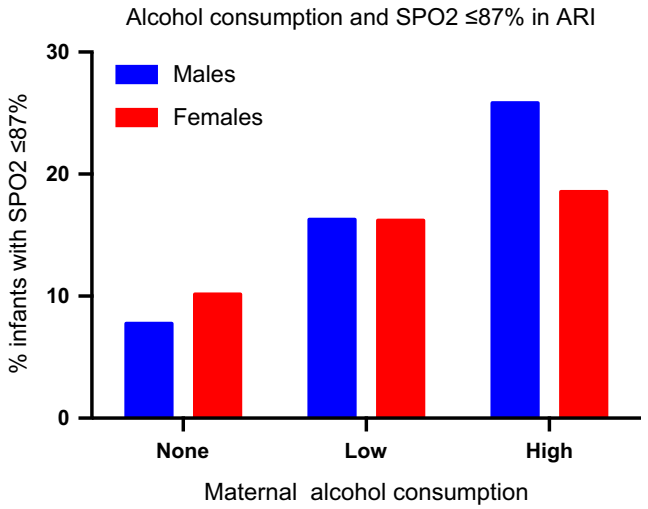

Figure 2 Proportion of patients with life-threatening (oxygen saturation ≤87%) acute respiratory infection (ARI) according to maternal alcohol consumption and gender.

Restricting these assessments to children with RSV infections confirmed with RT-PCR yielded similar results (Figures S1 and S2). Maternal alcohol consumption during the third trimester of pregnancy was associated with an increased risk for life-threatening RSV disease in hospitalised boys, but not in girls.

DISCUSSION

In this study, we report that mothers who admitted to even occasional consumption of alcohol during the last trimester of pregnancy exposed their infants to an increased risk of life-threatening ARI and that this effect was particularly strong for boys. Previous studies have shown detrimental effects of occasional alcohol intake on mental health in girls (8), and the risk of congenital anomalies has even been associated with low, sporadic doses of alcohol in both genders (25). Taken together, these findings suggest that abstinence seems to be the only safe recommendation for pregnant women. These observations, and previous findings on macronutrient intake during pregnancy and infant lung disease in our region (15), stress that maternal counselling during prenatal care can have an impact on behaviour that may affect infants' lungs.

The effects of alcohol intake on lung health are novel for infants but not unexpected. Ethanol exposure during late gestation in animal models has been seen to impair expression of pulmonary surfactant protein A, reduce ciliary beat frequency and dysregulate expression of the genes involved in host defence (14). Moreover, ethanol impairs phagocytic function and lung growth in neonatal mice (26) and affects terminal differentiation of interstitial and alveolar macrophages in neonatal guinea pigs (27).

The mechanism of differential gender susceptibility to alcohol is intriguing. Foetal lung development is a complex process that is tightly regulated by hormones (28). Alcohol-induced changes in maternal endocrine function can disrupt the normal hormonal interactions between the pregnant female and foetal systems, affecting the development of physiological functions in the foetus. Sexually dimorphic effects of alcohol consumption during pregnancy have been observed in both clinical and animal studies of the hypothalamic-pituitary-adrenal axis, a key player in the stress response mechanism (29). While the mechanisms behind the observed associations require further study, our data suggest that gender differences are not explained by a wide range of possible confounding factors known to influence paediatric lung disease. Moreover, no mediation effect was found for intrauterine growth retardation, birthweight or gestational ages, which have all been associated with prenatal alcohol intake (3,4).

Our study has some limitations. Firstly, as we questioned mothers about their past alcohol consumption while their children were in hospital, the accuracy of their recall may have been limited and this may have led to an under estimation of their actual alcohol intake. This limitation is inherent to the sample size of the study, requiring 56 560 children a year in our catchment area to detect 269 cases of life-threatening ARI. However, our data suggest that even admitting to *any* alcohol consumption during pregnancy should prompt the obstetrician to inform the mother about the potential detrimental consequences of such behaviour for her baby. Secondly, other unmeasured factors including illegal drug use may also have affected the observed outcomes and should be studied in the future. In fact, even though we controlled for a large number of potential confounders, alcohol intake is a complex behaviour and findings may always be affected by residual confounding,

including prenatal exposures, indicators of socio-economic status and post-natal factors. Therefore, these findings should be confirmed by additional studies. Thirdly, parents of a child with a severe infection might be more willing to report their risk behaviour to medical staff. However, this reporting bias would be applicable to the entire study population.

However, the study also has significant strengths. Firstly, we believe it is the first large hospital-based prospective study of ARI in infants and young children to examine the effects of foetal exposure to alcohol. Secondly, we controlled for a large number of relevant potential confounding factors. Thirdly, we used state-of-the-art laboratory techniques to identify RSV, which was the main respiratory pathogen in the hospitalised infants, and assayed for other relevant paediatric pathogens.

In summary, our study found that admitting to alcohol consumption during pregnancy, even at low levels, was associated with life-threatening ARI in boys younger than two years of age. Because this is a modifiable risk factor that is amenable to corrective interventions, further research is warranted to support public health strategies focused on prevention.

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FINANCIAL DISCLOSURE STATEMENT

The authors report no financial relationships relevant to this manuscript to disclose.

CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 Life-threatening RSV disease in infants and young children per maternal alcohol consumption: crude OR, low alcohol dose 2.61 (95% CI, 1.26–5.49) and high alcohol dose 4.61 (95% CI, 2.52–8.44) adjusted OR, low alcohol dose 5.33 (95% CI, 1.32–21.5) and high alcohol dose 22.68 (95% CI, 4.43–115.94) vs. non-consumption group in hospitalised boys.

Figure S2 Proportion of patients with life-threatening (oxygen saturation ≤87%) RSV disease according to maternal alcohol consumption and gender.

Table S1 Epidemiologic characteristics of the population.

Table S2 Other Risk factors for severe and life-threatening disease.