HHS Public Access
Author manuscript
Paediatr Respir Rev. Author manuscript; available in PMC 2018 January 01.

Published in final edited form as:
Paediatr Respir Rev. 2017 January ; 21: 34–37. doi:10.1016/j.prrv.2016.08.006.

In utero alcohol effects on foetal, neonatal and childhood lung disease

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Summary

Maternal alcohol use during pregnancy exposes both premature and term newborns to the toxicity of alcohol and its metabolites. Foetal alcohol exposure adversely effects the lung. In contrast to the adult "alcoholic lung" phenotype, an inability to identify the newborn exposed to alcohol *in utero* has limited our understanding of its effect on adverse pulmonary outcomes. This chapter will review advances in biomarker development of *in utero* alcohol exposure. We will highlight the current understanding of *in utero* alcohol's toxicity to the developing lung and immune defense. Finally, we will present recent clinical evidence describing foetal alcohol's association with adverse pulmonary outcomes including bronchopulmonary dysplasia, viral infections such as respiratory syncytial virus and allergic asthma/atopy. With research to define alcohol's effect on the lung and translational studies accurately identifying the exposed offspring, the full extent of alcohol's effects on clinical respiratory outcomes of the newborn or child can be determined.

Keywords

Foetal alcohol; pregnancy; newborn; immunity; lung; infection

Introduction

Despite the continued advances in studies focusing on the recognition of alcohol related birth defects (ARBD) including foetal alcohol spectrum disorders (FASD),[1] there remains a limited acknowledgment of the fact that *in utero* alcohol adversely effects multiple organs in the developing newborn, including the developing lung. This paper will highlight and update the current field of study into foetal alcohol's effect on the developing lung since our last review. [2] Our adult colleagues have made significant advances in deciphering the pathophysiology underlying the adverse effects of alcohol exposure on multiple cell types within the lung. Indeed, respiratory complications such as acute lung injury, adult respiratory distress syndrome (ARDS) and pneumonia are now well recognized sequelae of the

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Conflict of interest statement: The authors acknowledge that they have no financial disclosures to declare.

"alcoholic lung phenotype." [3,4] Due to impaired immune defenses of multiple cell types including alveolar macrophage, neutrophils and lymphocytes, adults with alcohol use disorders are more likely to develop serious pulmonary infections including bacterial and viral pneumonia.[5] Despite advances in understanding the adult immunocompromised "alcoholic lung," [6] there remains much to be learned to fully understand the complex consequences of *in utero* alcohol exposure during development on the lung.

We will review the continued prevalence of foetal alcohol exposure to premature and term newborns in our society and highlight the recent advances in the identification of this exposure during pregnancy using a variety of chemical biomarkers in various matrices. We will discuss recent advances in our understanding of the cellular injury specific to the developing lung exposed to alcohol *in utero*. Foetal alcohol's effect on immune defenses, particularly as they relate to the lung will be reviewed. We will summarize recent clinical updates evaluating foetal alcohol's effect on clinical respiratory outcomes, including bronchopulmonary dysplasia/death in the very low birthweight (VLBW) newborn, viral infection such as respiratory syncytial virus (RSV), and allergic asthma in neonates and children. Finally, we will highlight important areas for future investigations to identify and improve pulmonary outcomes of alcohol-exposed newborns and children.

Continued exposure of newborns, both term and preterm, to alcohol in utero

Despite persistent recommendations from healthcare workers and authorities such as the US Surgeon General, alcohol use during pregnancy in continues to place the developing fetus at risk for a variety of adverse birth outcomes. The National Birth Defects Prevention Study reported that 30% of women drank during their pregnancy while ~8.3% binge drank (> 5 drinks/sitting). [7] A recent report again noted that 30% of all pregnancies were complicated by maternal report of alcohol exposure. [8] Educational campaigns have clarified that there is no known "safe" level of alcohol consumption during pregnancy. Unfortunately, despite these efforts, the prevalence of alcohol consumption among pregnant women remains alarmingly high and was even higher among those with a college degree compared to those with less education. [9]

Although some reports fail to demonstrate a link between low to moderate drinking and the risk of premature delivery, others note an increased risk of preterm delivery with maternal alcohol use during pregnancy. [10,11] Multiple studies demonstrate that heavy or binge alcohol consumption increase the risk of premature delivery 2-3 fold, particularly in those less than 32 weeks gestation. [12-15] Therefore, some authors propose that extreme prematurity should be considered an alcohol-related birth defect. [14] Lester *et al* reported that ~30% of the mothers reported alcohol use during pregnancy in a very low birthweight (VLBW) newborn population.[16] Similarly, in a recent study of mothers who delivered VLBW (<1500 grams at birth) newborns admitted to the Neonatal Intensive Care Unit, we recently demonstrated that one third of the mothers admitted to alcohol use during pregnancy.[17]

It is important to recognize that maternal report of alcohol consumption during pregnancy inherently results in an under-representation of the true prevalence of alcohol use during pregnancy.[18-20] It is likely, therefore, that *in utero* alcohol exposure occurs in both premature and term newborns, and has the potential to adversely affect multiple developing organs. Although maternal drinking during pregnancy has been noted to decrease from the first trimester compared to the third trimester of pregnancy, organogenesis of multiple organ systems, particularly the lung and the developing immune system, remains vulnerable to the exposure to alcohol.

Advances in the identification of the alcohol exposed newborn

In an effort to eliminate the underreporting of alcohol exposure during pregnancy and bypass the need for maternal self-report, much research continues to focus on the development of accurate and clinically useful biomarkers of fetal alcohol exposure. Without accurate identification of the exposed newborn, either born prematurely or at term, advances in our understanding of the adverse effects of alcohol in organ systems such as the lung remain limited. Unlike adults with alcohol use disorders, typical laboratory biomarkers may not be optimal for identifying foetal alcohol exposure. Blood alcohol or direct oxidative metabolites such as acetaldehyde levels may not address long term intermittent foetal exposure in utero. Furthermore, routine blood tests such as gamma-glutamyl transferase, mean corpuscular volume, hemoglobin associated acetaldehyde, and carbohydrate deficient transferrin are not optimal during pregnancy.[21]

Thus, more sensitive biomarkers of non-oxidative alcohol metabolism have been investigated to more accurately identify the alcohol-exposed newborn. Non-oxidative metabolites of alcohol can be detected for prolonged periods in various matrices such as meconium, hair, fingernails, umbilical cord tissue, placenta, and newborn blood. Fatty acid ethyl esters (FAEEs) in meconium have been the most extensively investigated biomarkers of *in utero* alcohol exposure and their elevation can predict cognitive deficits in the exposed newborn. [22] The investigation and validation of other non-oxidative metabolites of alcohol such as ethyl glucuronide (EtG), ethyl sulfate (EtS), phosphatidylethanol (PEth), or their combination remain the focus of extensive research. [23-26] Indeed, PEth has been demonstrated as a valid and stable biomarker of previous alcohol exposure and can be detected on dry blood spot samples. [27]

While the literature has largely remained focused on developing biomarkers to identify foetal alcohol exposure to term newborns, there remains a paucity of data regarding the identification of alcohol exposure in premature newborns. We recently reported that the placenta, a non-invasive and easily obtainable tissue source, demonstrated elevated FAEEs in VLBW exposed to alcohol *in utero*. [17] Additionally, we also found that the FAEE ethyl linolenate was significantly elevated in the meconium of alcohol-exposed VLBW premature newborns.[28] Finally, in a guinea pig model of foetal ethanol exposure, we demonstrated accumulation of FAEEs in the lung tissue of the newborn guinea pigs exposed to ethanol *in utero*. [29] Whether additional matrices, such as amniotic fluid, lung (tracheal aspirate) fluid or meconium can be sources for biomarker(s) to accurately identify alcohol exposure in the understudied premature population requires further investigations.

Thus, continued evaluations using translational studies of premature and term newborns as well as animal models of foetal alcohol exposure are necessary to determine the validity of a biomarker panel. The goal of such studies would ultimately be to develop a sensitive and reliable panel of biomarker(s) that could be utilized in the clinical arena. Accurately determining both the amount of alcohol exposure and the time of gestational development during exposure in both term and premature newborns would allow advancement in our understanding of its potential adverse consequences to the developing lung.

Alcohol-induced cellular injury to the developing lung

Foetal alcohol exposure increases lipid peroxidation products, lipid peroxidation adduct formation on proteins, and DNA oxidation in multiple organs. [2] Specifically for the developing lung, research continues to demonstrate alcohol-induced cellular injury in multiple animal models, suggesting that alcohol exposure alters lung development. In mice, acute alcohol administered mid-gestation increased histone acetylation in the developing lung resulting in apoptosis of both mesenchymal and epithelial cells. [30] Furthermore, early administration of alcohol to pregnant mice caused significant DNA damage in the foetal mouse lung. [31] Reductions in surfactant protein-B (SP-B) and altered surfactant phospholipid composition have been reported in multiple models including rat [32] and sheep, [33,34] suggesting direct effects on the epithelial cells of the developing lung. Finally, in these models, increased collagen type III alpha1 gene [32] and increased collagen deposition [34] were also demonstrated in exposed pup lungs, suggesting fibroblast alterations with alcohol exposure. These data, taken together, suggest that *in utero* alcohol exposure alters multiple cell types in the developing lung and could potentially increase the risk of respiratory distress in the newborn. The interesting findings of increased collagen in the alcohol-exposed lung raises the possibility that foetal alcohol exposure could result in altered pulmonary dynamics and increase the risk of lung scarring lesions such as bronchopulmonary dysplasia in the exposed offspring.

In utero alcohol and altered immune defenses

Multiple animal models suggest that *in utero* alcohol exposure deranges the immune defense in the developing lung. [35] In sheep models, foetal alcohol exposure resulted in reduction of the collectins SP-A [33,34] and SP-D [36] and alters baseline pro-inflammatory cytokine mRNA expression in the exposed neonatal lung. [33,37] We have demonstrated in multiple animal models that *in utero* alcohol suppresses the maturation and function of the resident alveolar macrophage (AM), increasing the risk of bacterial infection. [38] This altered AM immune defense is modulated by alcohol-induced mitochondrial oxidant stress and mitochondrial dysfunction. [39,40] Given that FAEEs are a reliable biomarker of alcohol exposure and accumulate in the neonatal lung after foetal alcohol exposure, [29] we recently evaluated the direct effects of these compounds on the neonatal AM. We hypothesized that FAEEs would impair mitochondrial functioning and in-part contribute to AM dysfunction observed with alcohol exposure. Indeed, we demonstrated that FAEEs such as ethyl oleate directly injure the neonatal AM, causing mitochondrial oxidative stress, apoptosis and cellular dysfunction. [29] Direct effects of FAEE on other cell types within the developing lung remain unexplored.

Whether AM dysfunction and the risk of bacterial infection persists beyond the neonatal period in the foetal alcohol exposed lung is unknown. Previous studies have demonstrated that after foetal alcohol exposure, adult animals continued to demonstrate impaired adaptive immunity, [41] and an increased risk and severity of pulmonary influenza infection. [42] Former premature newborns and infants are at increased risk for viral infections, particularly respiratory syncytial virus (RSV). Investigators evaluating the pathogenesis of RSV using a lamb model suggest that foetal alcohol exposure may further increase neonatal susceptibility to this viral infection. [43]

Foetal alcohol exposure and risk of adverse pulmonary outcomes

We have noted recent advances in defining *in utero* alcohol's effect on multiple cell types within the developing lung using multiple experimental animal models. However, unlike our adult colleagues,[4-6] clinical studies defining foetal alcohol-induced pulmonary effects in newborns and children remain limited. As previously noted, scientific progress in this regard remains limited, in part due to the inability to accurately identify the alcohol-exposed newborn or child. We have previously demonstrated that maternal alcohol exposure during pregnancy was associated with an increased risk of infection in both term [44] and premature newborns. [45] In a recent study, we evaluated VLBW premature newborns admitted to the Neonatal Intensive Care Unit and identified *in utero* alcohol exposure via maternal self-report after delivery. In this cohort (n=143), maternal alcohol use was associated with an increased odds of BPD/Death in the premature newborn.[46] Furthermore, similar to our earlier work in term newborns, [44] heavy maternal drinking (≥7 drinks/week) was associated with increased odds of developing late onset sepsis (LOS) in the VLBW. [46] Although the sample size evaluated was small, the data strongly suggest that additional clinical investigations with larger numbers are warranted to evaluate alcohol's association with adverse pulmonary outcomes such as BPD or associated LOS in the VLBW newborn.

Given the compelling animal and adult data regarding alcohol exposure and risk of infection, including pulmonary viral infection, researchers in Argentina recently evaluated whether maternal alcohol consumption during pregnancy increased the risk of life threatening respiratory infections in children < 2 years of age. Alcohol exposure during pregnancy was determined via maternal self-report at the time of the child's hospitalization. In this study, alcohol consumption was associated with an increased risk of life threatening respiratory infections (particularly RSV infection) in boys.[47] Such clinical reports and animal data [43] emphasize and justify the need for continued investigations evaluating whether *in utero* alcohol exposure increases the risk of respiratory viral infections such as RSV in the exposed infant or child.

Although it has long been demonstrated that *in utero* alcohol exposure increases cord blood IgE,[48] investigations continue to assess whether foetal alcohol exposure alters the risk of atopy and/or asthma in the exposed child. In a recent report evaluating a Japanese cohort, maternal alcohol intake during pregnancy significantly increased the risk of atopic eczema before age 3 and before age 5. [49] These data are in agreement with other authors, who demonstrated an increased risk of atopic dermatitis in early infancy [50] and during the first 7 years of life in alcohol-exposed offspring. [51] Nevertheless, the data on foetal alcohol's effect on the development of asthma is less convincing. In the Japanese cohort, offspring exposed to maternal alcohol demonstrated a 2 fold, albeit non-significant (p=0.058) increased risk of asthma before age 3, suggesting further studies are warranted. [49] However, in a large Norwegian cohort, maternal alcohol use during pregnancy had no significant effect on asthma at age 3 or age 7, [52] while a study of newborns in Copenhagen demonstrated no effects of alcohol exposure on infant lung function testing at one month of age. [53]

Conclusions

In summary, despite continued foetal alcohol exposure to both term and premature newborns, the clinical awareness of such exposure and our clinical ability to accurately identify the exposed newborn remains lacking. Continued advances in biomarker development using animal models and translational investigations hold the key to accurate identification of the alcohol-exposed newborn born either prematurely or at term gestation. By ascertaining alcohol's effect on multiple cell types within the developing lung and accurately identifying the exposed offspring, the full extent of alcohol's effects on clinical respiratory outcomes, including bronchopulmonary dysplasia and infectious pulmonary complications of the newborn or child will be determined. Although significant progress has been made in understanding the effects of chronic alcohol on the adult "alcoholic lung," further research into the "developing alcoholic lung" is required since exposure (amount and timing) is superimposed on development. As such, we cannot assume the alterations demonstrated in the adult alcoholic lung will be evident in newborns exposed *in utero* or in children after such *in utero* exposure. Additionally, further investigations are needed to increase our understanding of the effects of alcohol's metabolites such as FAEE on cell injury in multiple developing organs including the lung. [22] Finally, determining whether therapeutic approaches currently under investigation in adults exposed to alcohol, such as antioxidant replacement or zinc replacement therapy [54] could also be applicable and benefit the exposed newborn lung requires full investigation.

Acknowledgments

Supported in part by NIH 1 P50 AA 135757 Emory Alcohol and Lung Biology Center.

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Educational Aims

- To stress the continued, yet often unrecognized incidence of foetal alcohol exposure in both premature and term newborns.
- To review the advances in biomarker(s) development to assist in the accurate identification of the alcohol exposed premature and term newborn.
- To explore the current understanding of the pathophysiological effects of alcohol exposure on the developing lung.
- To review the latest data evaluating the association between *in utero* alcohol exposure and clinical respiratory outcomes of the newborn and child including bronchopulmonary dysplasia, viral infection and allergic asthma.

Future Research Directions

- The continued development of accurate biomarker panels for the identification of both premature and term newborns exposed to alcohol in utero.
- Determine the mechanisms underlying the effects of *in utero* alcohol and its metabolites on multiple cell types of the developing lung.
- Translational studies to further define the associations between *in utero* alcohol exposure and neonatal and childhood lung diseases.
- Evaluate potential therapeutic interventions for the alcohol-exposed newborn at risk for adverse pulmonary outcomes.