Paediatric Respiratory Reviews 21 (2017) 34–37

Contents lists available at ScienceDirect

Paediatric Respiratory Reviews

Mini-Symposium: Maternal Diseases effecting the newborn

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

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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.

ARTICLE INFO

Keywords:
Foetal alcohol
pregnancy
newborn
immunity
lung
infection

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 paper 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.

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 "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

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http://dx.doi.org/10.1016/j.prrv.2016.08.006

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 underrepresentation 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