

Effects of Maternal Alcoholism on Placental Function and Lung Fetal Development

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Rec date: Aug 20, 2014; Acc date: Sep 25, 2014; Pub date: Sep 27, 2014

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Abstract

Epidemiological and clinical data indicate that alcohol consumption during pregnancy remains a substantial public-health problem as many pregnant women continue to drink alcohol despite clinical recommendations and public health campaigns warning about the risks associated. It is well known that maternal ethanol consumption during pregnancy results in deleterious effects on the developing fetus. Among these effects is the so called Fetal Alcohol Spectrum Disorder (FASD). Fetal Alcohol Syndrome (FAS) is a severe form of FASD and also an irreversible condition. Although all children born to alcoholic mothers show abnormalities, in some cases these may not be clearly observable. There is a wide spectrum of abnormalities regardless of the amount and pattern of alcohol exposure, differences in maternal, foetal and placental metabolism of ethanol/acetaldehyde, as well as genetic factors. In this article we present some of the effects of maternal alcoholism on placental functions and how it affects lung development.

Introduction

Alcohol is one of the most common teratogenic agents and its uncontrolled consumption during pregnancy has been widely associated with adverse effects in the developing fetus, including premature birth, low birth weight, multiple birth defects, and neurodevelopmental disorders, collectively named Fetal Alcohol Spectrum disorder (FASD). There is a severe form of FASD, namely Fetal Alcohol Syndrome (FAS), which is an irreversible condition. This syndrome, first described by Jones and Smith [1], is characterized by intrauterine growth retardation (IUGR), a characteristic pattern of abnormal facial features, physical and mental retardation as well as important defects in cardiac and lung development. FASD is currently used to describe a lesser degree of deformities associated to FAS, sometimes unnoticeable except by close examination. Despite abundant public health campaigns and clinical recommendations about the risks associated with alcohol intake during pregnancy, many pregnant women continue to abuse alcohol consumption.

Placental Functions and Oxidative Stress

The placenta is the transient organ where the physiological exchange of metabolites between mother and fetus occurs. Its function is to deliver nutrients to the fetus, to excrete waste products into the maternal blood stream and to modify, via hormones, the maternal metabolism at different stages of pregnancy. Therefore, it is reasonable to assume that the placenta fulfills the role of lungs, gastrointestinal tract, kidney and liver, as well as an endocrine organ for the fetus. The events that characterize normal placental growth are considered to be important determinants of fetal growth and development). All of these events are likely interrelated and susceptible to the effects of many environmental factors (Table 1) [2].

| Structure studied | Evidences | Conclusions | References |
|---|---|---|--|
| Human Placenta | Acetaldehyde induce oxidative stress and reaches the foetus either by placental production or by placental transference | Oxidative stress affects foetal and placental growth and alters placental metabolic functions | Henderson et al. [3] Bosco [4] Ornoy [5] Bosco and Díaz [2] |
| Rat Placenta | Impaired EVT motility and its invasiving functions | Inadequate placentation in the rat | Gundogan et al. [6], Pijnenborg et al. [7] |
| Isolated alcohol perfused human placental cotyledon | Impairment in the transfer of fetal nutrients such as glucose, amino acids and zinc | Direct placental toxicity | Fisher and Karl [8] |
| Perfused ethanol human placental villous | Decreased nitric oxide release | Adverse effect on placental blood flow | Kay et al., [9] Myatt L, Cui X [10] |

Table 1: Placental fetal effects of maternal alcohol ingest in pregnancy

It is important to note that as the human fetal-placental vasculature lacks autonomic innervation, autocrine and/or paracrine agents, such as the NO radical, play an important role in the regulation of fetal-placental blood flow [10], (Table 1). In addition, in anchoring placental villi, the cytotrophoblasts generate an invasive extra villous trophoblasts (EVT) that later migrate into the decidua and remodels the endometrial spiral arteries to produce the low-resistance vascular system that is essential for fetal growth (Table 1) [7].

Placental development is a highly regulated process and is therefore quite susceptible to disruption. Foreign compounds, such as alcohol, may interfere with placental functions on many levels, including cell signaling, production and release of enzymes and hormones, transfer of nutrients and waste products, cellular growth and maturation and in delivery. It is well known that the third trimester of pregnancy is when alcohol exerts its greatest impact on fetal growth [11]. The most plausible hypothesis whereby alcohol decreases prenatal growth, is via hypoxia (Table 1), which interferes with cellular processes that require oxygen, such as placental transport and protein synthesis [2,4].

Maternal ethanol ingestion may cause fetal injury, in particular, impairing somatic and brain growth through at least two mechanisms: (1) directly, by fetal toxicity from ethanol and/or acetaldehyde [3], (2) (indirectly, by ethanol induced placental injury [12] and selective fetal malnutrition (Table 1) [8]. In vivo and in vitro experiments have demonstrated that transient ethanol exposure causes oxidative stress both in rat placenta [6,13] and in human placental villous tissue (Table 1) [9]. Additionally, oxidative stress constitutes the general mechanism of injury on placental pathology. Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the ability of the biological system to readily detoxify intermediate ROS or to easily repair the resulting damage [14,15]. The mechanism of oxidative stress seems to operate in alcohol ingest pregnancy [5].

Deleterious Effects of Alcohol Exposure on Lung Development

There have been reports of a higher incidence of respiratory problems in children who were exposed to alcohol in intrauterine life, so the knowledge regarding the effects of prenatal exposure to alcohol on pathophysiological effects to the vulnerable developing lung is crucial to develop precise and consistent methods for identifying pregnancy alcohol exposed infants [16].

Fetal lung development is a complex process, which is tightly regulated, in part, by hormones and growth factors [17] such as vascular endothelial growth factor (VEGF). In addition, VEGF is an endothelial cell-specific mitogen that promotes tissue vascularisation. In the developing lung VEGF is critical for angiogenesis, endothelial cell maturation and alveolar formation (Table 2) [18]. These authors found a decrease in the VEGF expression in the fetal lungs of pregnant ewes exposed to alcohol during the last trimester of pregnancy.

| Structure studied | Evidences | Conclusions | References |
|--|---|--|---|
| Fetal lungs of pregnant ewes | Impaired expression of pulmonary surfactant protein A, as well as decrease in the VEGF expression in the fetal lung | Alterations in fetal lung maturation and immunity | Lazic et al. [18,19] Giliberti et al.,[16] |
| Mouse embryonic and adult lung tissues | Class I and IV ADH isozymes metabolize ethanol and retinol | High levels of ethanol inhibit retinol metabolism altering the normal development of epithelial lung tissues | Ang et al., [20] |

| | | | |
|--|--|---|----------------------|
| Foetal lungs from pregnant guinea pig exposed to alcohol and Streptococcus pneumonia | Deficient alveolar macrophage phagocytosis | Increase risk of pulmonary infection after birth | Sozo et al.,[21] |
| Foetal lungs of ethanol exposed pregnant guinea pig | Impairment in extracellular matrix deposition and surfactant protein gene expression | Increased risk of respiratory distress syndrome after birth | Gautier et al., [22] |
| Fetal lung of ethanol exposed pregnant mice | Weight decrease and higher expression of Hoxb5 in the saccular phase of lung development | Alterations on lung development | Wang et al.,[23] |

Table 2: Fetal lung effects of maternal alcohol ingest in pregnancy

In another line of evidence, it has been demonstrated that when the mother has moderate ingest of alcohol, class I and class IV alcohol dehydrogenase metabolize the alcohol in the developing fetal lung (Table 2) [20]. But the developing lung has weakly developed antioxidant systems, so they are particularly vulnerable to alcohol induced oxidative stress and antioxidant depletion (Table 2) [21,22].

In addition, surfactant lipoproteins A and D are important components of pulmonary innate immunity and have an essential role in pulmonary defense against inhaled pathogens [19]. In the lung, these surfactant proteins are produced and secreted by alveolar type II cells and by non-ciliated bronchial and bronchiolar epithelial cells (Clara cells). These surfactants are a mixture of phospholipids whose function is to prevent alveolar collapse during end-expiration [24] due to its role in reducing surface tension. Its deficiency underlies the pathophysiology of respiratory distress syndrome in premature newborns. Ethanol exposure significantly alters at least some of these innate responses in the lung [19] and, as a consequence, ethanol produces an imbalance between reactive oxygen species and antioxidants, as well as increasing the burden of reactive oxygen species that can lead to protein oxidation, lipid peroxidation and mutations due to DNA oxidation [16].

Alterations in neonatal lung development as a consequence of fetal alcohol exposure have been demonstrated in multiple animal models. During normal lung development, Hoxb5, a homeobox-containing gene, has been shown to be important in the patterning of airway branches during mouse lung morphogenesis [25]. In mice, fetal exposure to alcohol during the second trimester (at the pseudo glandular stage of lung development) resulted in decreased lung mass and delayed lung maturation [23]. This was due to a persistent expression of Hoxb5, instead of the necessary decrease for normal bronchiole elongation during the saccular phase of development, (Table 2). Also, Giliberti et al., [16] demonstrated that in utero alcohol exposure alters the development of the immune system and decreases pulmonary defenses against both bacterial and viral infection, so newborns have an increased baseline risk for pneumonia, (Table 2). In addition, Gauthier et al., [22,26] showed an increased risk for pneumonia in fetal alcohol exposure in guinea pig animal models.

Final Remarks

In conclusion, in utero alcohol induces placental oxidative stress, and as a consequence, a concomitant release of ROS into the developing lung fetus. These events are related to a decreased expression of the angiogenic factor VEGF, a depletion of the antioxidant system, a deficiency in surfactant production, and a decrease for normal bronchiole elongation (Tables 1 and 2). All this events are particularly important in at-risk premature newborn. Further research is required to fully understand the effects of in utero alcohol exposure on infection risks and infectious-mediated pulmonary morbidities.

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