Pulmonary hypoplasia is a substantial cause of death in newborn infants, and oligohydramnios is one of the most commonly associated abnormalities. Lung growth is influenced by physical factors such as the intrauterine space, lung liquid volume and pressure, and fetal breathing movements. During lung development, the main physical force experienced by the lungs is stretching induced by breathing movements and the lung fluid in the airspaces. Oligohydramnios reduces the intrathoracic cavity size, thus disrupting fetal lung growth and leading to pulmonary hypoplasia. The exact mechanism by which oligohydramnios alters the respiratory system structure and the effect of oligohydramnios on long-term respiratory outcomes remain unknown. In this review, we summarize the effects of oligohydramnios on lung development, discuss the mechanisms of oligohydramnios-induced pulmonary hypoplasia identified in various animal studies, and describe the long-term respiratory outcomes in childhood of oligohydramnios-exposed fetuses reported by a population-based study.

Key Words:
alveolarization;
collagen;
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Pulmonary Hypoplasia Induced by Oligohydramnios: Findings from Animal Models and a Population-Based Study

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1. Introduction

Pulmonary hypoplasia is a developmental anomaly characterized by underdevelopment of the lung tissue and is a common finding (up to 22%) in neonatal autopsies.1 Pulmonary hypoplasia secondary to congenital diaphragmatic hernia, oligohydramnios, and renal agenesis is a major cause of neonatal morbidity and mortality. Anionic fluid is produced from maternal plasma and secreted from the fetal membranes. Fetal urine contributes to the amniotic fluid when the fetal kidneys start to function. Brace et al2 produced from maternal plasma and secreted from the cause of neonatal morbidity and mortality. Amniotic fluid is hernia, oligohydramnios, and renal agenesis is a major pulmonary hypoplasia secondary to congenital diaphragmatic pertension and air leaks.5 Currently, management of the risk of acute respiratory morbidity such as pulmonary hypoplasia-induced pulmonary hypoplasia.6 The exact mechanism by which oligohydramnios induces lung hypoplasia and alters the respiratory system structure remains unknown. An understanding of the molecular and pathophysiological processes controlling fetal lung growth and development during oligohydramnios holds potential for developing novel therapies for preventing and treating oligohydramnios-induced pulmonary hypoplasia.

2. Normal lung development

Studies have supported the use of rodents for studying oligohydramnios because their alveolarization phase resembles that of humans (Figure 1).7 Lung development begins as a ventral outpouching of endodermal cells from the anterior foregut into the surrounding mesenchyme at 9.5 days postconception (E9.5) in mice. This ventral diverticulum grows caudally to form the primitive trachea and subsequently divides to form two lung buds. During the pseudoglandular phase (E9.5–E16 in mice; 6–16 weeks gestation in humans), the lung buds undergo repeated dichotomous branching to form the bronchiolar epithelium, respiratory bronchioles, and alveolar ducts. Paracrine factors produced by the surrounding splanchnic mesenchyme are essential for the dichotomous branching of the bronchiolar epithelium during this phase of development. Between 16 days and 17 days postconception in mice (canalicular phase in mice; 16–26 weeks gestation in humans), the rapid growth rate of lung tissue declines and dichotomous branching is completed. This phase is characterized by the onset of capillary growth within the developing lung and by the appearance of type II cells containing lamellar bodies, the cellular organelles that comprise lung surfactants. During the saccular phase of lung development (E17–birth in mice; 26–36 weeks gestation in humans), the capillaries continue to grow, and the distal lung is remodeled to resemble the adult lung parenchyma. This remodeling includes the sustained growth of capillary networks, cellular differentiation, thinning of mesenchyme-derived stroma, and expansion of the developing alveoli.8

Physical forces are crucial for regulating fetal lung growth and maturation.9 Distended pressure formed by lung fluid within the airways is the primary physical force stimulating the lungs during normal lung development.10 Furthermore, the fetus exhibits episodic fetal breathing movements (FBMs), which are accepted as part of normal human lung development;11,12 According to changes in thoracic shape, Kitterman12 speculated that FBMs result in repetitive changes in the distal lung surface area by ~5%. Functional maturation of pulmonary alveolar epithelial cells was promoted by lung stretch at various degrees in experiments involving fetal rat lungs and type II epithelial cells.13 Drainage of lung fluid in fetal sheep or elimination of FBMs by cervical cord transection in the rabbit fetus leads to lung hypoplasia.14,15 Hence, distended pressure generated by lung fluid and cyclic stretch of the lung are the two major determinants of normal fetal lung development.

3. Effects of oligohydramnios on growth factor expression

Lung growth and development require extrinsic factors and mechanical forces.12,13,14 Experimental tracheal ligation in fetal lambs indicated that the fetal lung liquid volume is vital for lung development.17 Additionally, several in vitro and in vivo studies have suggested that FBMs regulate lung growth by activating growth factor expression.18 Platelet-derived growth factor (PDGF) is a powerful stimulator of fibroblast chemotaxis and proliferation and is crucial for the alveolarization of normally developing lungs.19–21 PDGFs are homodimers or heterodimers comprising two distinct polypeptide chains (A and B), which can be dimerized via sulfhydryl bridges to form three bioactive isoforms (AA, BB, and AB).22 Studies have demonstrated that mechanical strain on the lungs increases PDGF production and activates PDGF receptors in vascular smooth muscle cells.23 Souza et al24,25 used antisense oligonucleotides in an embryonic rat lung explant culture and reported that PDGFs play critical roles in early lung growth and branching morphogenesis.

PDGF-A and its receptor are essential in lung elastogenesis and alveolarization.26 Haider et al27 found that the absence of elastic tissue in hypoplastic human fetal lungs...
was associated with oligohydramnios. Before alveolarization in the developing lung, elastin is deposited in the mesenchyme surrounding the developing distal airways. During alveolarization, elastin is deposited at the apex of the secondary septal crests. Oligohydramnios induced at the pseudoglandular stage of lung development reduced elastin deposition, alveolarization, and the expression of PDGF and its receptors in a rat model.

Connective tissue growth factor (CTGF) is involved in fibroblast proliferation, cellular adhesion, and extracellular matrix synthesis. Moreover, CTGF contributes to collagen deposition during downstream expression of transforming growth factor (TGF)-β1, which stimulates collagen synthesis in human embryonic lung fibroblast cultures. A previous study showed that mechanical-stretching-induced type I collagen mRNA expression is blocked by anti-TGF-β1 neutralizing antibodies in cultured rat mesangial cells. Oligohydramnios induced on Day 19 and Day 21 of gestation was shown to reduce TGF-β1 expression, lung collagen levels (type I collagen), and level of tissue inhibitor of metalloproteinase (TIMP)-1 proteins, but nevertheless, it increased matrix metalloproteinase (MMP)-1 concentrations. In addition, there was no difference in CTGF expression between control and oligohydramnios-exposed rats. These data indicated that no autocrine loop of CTGF is involved in the signaling cascade induced by oligohydramnios and that downregulation of collagen synthesis might be related to the pathogenesis of oligohydramnios-induced respiratory morbidity.

Vascular endothelial growth factor (VEGF) is a potent endothelial cell mitogen that regulates endothelial cell differentiation and angiogenesis. Angiogenesis is physiologically crucial for alveolarization during normal lung development. Oligohydramnios induced at the pseudoglandular stage of lung development reduced angiogenesis and did not significantly reduce VEGF expression in a rat model. These studies suggest that the development of the pulmonary vasculature is complex and that other angiogenic factors are involved in regulating fetal lung angiogenesis.

Alveolar development in mice treated with an angiogenesis inhibitor could be maintained after vitamin A supplementation. Vitamin A treatment improved lung development in ventilated preterm lambs by increasing the expression of VEGF and its receptor. An in vitro study suggested that exogenous retinoic acid may enhance lung alveolarization by activating fibroblast proliferation via PDGF. Nevertheless, VEGF expression and fetal lung development were not enhanced after maternal retinoic acid treatment in oligohydramnios-exposed fetal rat lungs. Therefore, additional studies are warranted to clarify the reasons for discordance among these studies, such as a stage-specific requirement for retinoic acid during lung development.

4. Oligohydramnios reduces collagen and elastin expression

Collagen fibrils, which are important for maintaining the normal lung structure, are distributed widely in the alveolar interstitium, the bronchial lamina propria, the interlobular septa, and the interstitium of the bronchial tree. Elastin is also a vital structural component of the lung, enabling the expansion and recoil of the pulmonary parenchyma. Elastin is deposited at the apex of the secondary septal crests during alveolarization, and on the mesenchyme surrounding the developing distal airways before alveolarization in the developing lungs. Elastin haploinsufficiency adversely affects pulmonary angiogenesis, resulting in lung growth arrest and impaired respiratory function.

During the pseudoglandular stage of lung development, lung collagen I expression and the collagen level were shown to decrease in fetal rats exposed to maternal oligohydramnios. Additionally, the absence of elastic tissue in hypoplastic human fetal lungs is associated with maternal oligohydramnios. A balance between collagen synthesis and degradation is achieved through the de novo synthesis of collagen, inhibition of MMP activity by tissue TIMPs, and proteolytic degradation by MMPs. Activation of metalloproteinase can be induced by an imbalance in MMP and TIMP levels. Collagen degradation in intrathoracic spaces is stimulated by a higher level of MMP than TIMP, which is induced by maternal oligohydramnios, in fetal rat lungs. Altered extracellular matrix content caused by maternal oligohydramnios, which is found in fetal rat lung models, might correspond to the altered respiratory function of the offspring.

5. Effect of oligohydramnios on respiratory outcomes in children

Lindner et al. observed that neonates exposed to oligohydramnios experienced short-term respiratory morbidity and tended to experience more air leaks than did healthy neonates. A small case–control study found that infants exposed to prolonged oligohydramnios born following the preterm premature rupture of the membranes prior to 25 weeks gestation were at a high risk of prolonged initial hospitalization and major respiratory morbidity in their first 2 years of life. However, the long-term effects of oligohydramnios on the respiratory system are unknown. In a retrospective cohort study, Chien et al. observed that oligohydramnios-exposed children had an 8% higher incidence rate of respiratory hospitalization (ICD-9-CM: 493, 494, 496, 512, 518, 786.00, 786.05, 786.07, 786.09, 786.1–786.4, 799.02, or 799.1, 466, 480–487, 490, 491, 510, or 513, 786) and tended to experience more air leaks than did healthy neonates. This risk remained following adjustment for neonatal characteristics, parental demographics, insurance eligibility group, urbanization level of insurance registration area, level of prenatal care, and maternal risk factors. The findings of this study provide useful clinical implications, especially for risk and prognosis evaluation, management adjustment, and education on respiratory outcomes for parents of maternal oligohydramnios-exposed children.

Pulmonary hypoplasia, which can be induced by maternal oligohydramnios in human fetuses, is associated with decreased lung function in infants. However, the
underlying mechanism by which oligohydramnios alters the respiratory system and its effects on long-term respiratory outcomes remain unclear. According to a series of studies with an established animal model and a population-based study, a schematic diagram illustrating prenatal exposure to oligohydramnios and the implications for subsequent respiratory disease is provided in Figure 2.

6. Conclusions

Rats subjected to oligohydramnios on Day 16 of gestation exhibited lung hypoplasia and a marked decrease in extracellular matrix expression. Similarly, decreases in PDGF and TGF-β1 expression were observed on Day 19 and Day 21 of gestation. Concomitant treatment with maternal retinoic acid increased PDGF expression but did not enhance fetal lung development. In a matched retrospective cohort study, oligohydramnios-exposed children had a higher incidence rate of respiratory illnesses and were associated with increased healthcare use. Additional basic translational and clinical studies are warranted in the fields of oligohydramnios, pulmonary dysplasia, and extreme prematurity because the incomplete development of the lungs was shown in our investigations to share a common set of features. For example, maternal or postnatal vitamin A administration during the canalicular stage of lung development in oligohydramnios-exposed offspring. Developing effective strategies for preventing or treating pulmonary dysplasia induced by maternal oligohydramnios can improve prognosis and reduce the rate of respiratory morbidity in these children.

Conflicts of interest

The authors have no conflicts of interest relevant to this article to declare.

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