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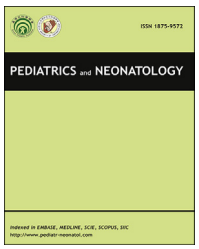

REVIEW ARTICLE

Pulmonary Hypoplasia Induced by Oligohydramnios: Findings from Animal Models and a Population-Based Study

Chun-Shan Wu [a], Chung-Ming Chen [b,c,*], Hsiu-Chu Chou [d]

[a] *Department of Pediatrics, Shuang Ho Hospital, Taipei Medical University, Taipei, Taiwan*
[b] *Department of Pediatrics, Taipei Medical University Hospital, Taipei, Taiwan*
[c] *Department of Pediatrics, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan*
[d] *Department of Anatomy and Cell Biology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan*

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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.

* Corresponding author. Department of Pediatrics, Taipei Medical University Hospital, 252, Wu-Hsing Street, Taipei 110, Taiwan.
E-mail address: cmchen@tmu.edu.tw (C.-M. Chen).

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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. Amniotic 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 al[2] found that fetal swallowing of amniotic fluid regulates the amniotic fluid volume in late-gestation sheep. Oligohydramnios may restrict fetal lung growth and can result in pulmonary hypoplasia in experimental animal models and human fetuses with prolonged rupture of the fetal membranes.[3,4] Neonates exposed to oligohydramnios caused by the premature rupture of the membranes have an increased risk of acute respiratory morbidity such as pulmonary hypertension and air leaks.[5] Currently, management of the condition is primarily supportive, and specific treatments designed for accelerating lung development are lacking.[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 bronchioles, 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]

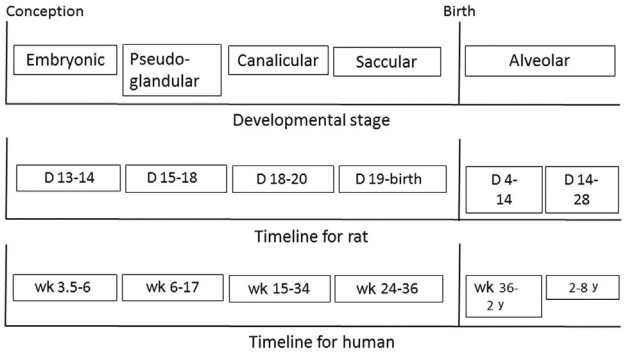

Figure 1 Timeline for lung development in the mouse, rat, and human respiratory systems.

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, Kitterman[12] 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.[12,13,16] 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 al[24,25] 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 al[27] found that the absence of elastic tissue in hypoplastic human fetal lungs

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