Intrauterine inflammation: effects on fetal lung development

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Intrauterine infection or inflammation is common in cases of preterm birth, especially those that occur at very early gestational ages. Exposure of the fetus to prenatal infection or inflammation is independently associated with alterations in the risk of several neonatal diseases associated with prematurity. For example, evidence of exposure to infection/inflammation before birth is associated with a reduction in the risk of neonatal respiratory distress syndrome (RDS). This life threatening disease, which accounts for many neonatal deaths, is believed to be due primarily to a lack of pulmonary surfactant. The association between intrauterine inflammation and reduced risk of RDS suggests that prenatal inflammation stimulates fetal pulmonary surfactant production. In studies using sheep we have shown that experimentally induced intrauterine inflammation or infection (induced by amniotic fluid injection of lipopolysaccharide or live ureaplasmas) causes a precocious increase in pulmonary surfactant in the preterm lungs (Moss *et al.*, 2002a; Moss *et al.*, 2008) that improves preterm lung function, consistent with observations of human preterm infants. The effects of intrauterine inflammation appear to result from direct action of proinflamatory stimuli on the fetal lungs (Moss *et al.*, 2002b) rather than by systemic signals, such as stimulation of the fetal hypothalamic-pituitary-adrenal axis and activation of the classical glucocorticoid-mediated lung maturation pathway (Notsos *et al.*, 2002). These initial experiments have focused investigation of responsible mechanisms on local pulmonary factors that might be induced by inflammation and stimulate surfactant production.

A prime candidate for mediating inflammation-induced surfactant production by the preterm lung is prostaglandin E_2 and/or other arachidonic acid metabolites. Prostaglandin E_2 is a fundamental mediator of inflammation; limited available evidence indicates it can induce surfactant production in preterm lungs. Our experiments demonstrate that intrauterine inflammation induces expression of enzymes responsible for prostaglandin production in fetal lung tissue. Lung tissue analyses from these same experiments have demonstrated also that paracrine/autocrine production and/or metabolism of glucocorticoids in fetal lung tissue may occur in response to inflammation, as a result of inflammation-induced changes in expression of 11β hydroxysteroid dehydrogenase (types 1 and 2). This effect might account for at least some of the changes in fetal lung development induced by inflammation.

In order to address the role of glucocorticoid signaling in the response of the fetal lungs to inflammation, we are inducing intrauterine inflammation in transgenic pregnant mice carrying glucocorticoid receptor knockout fetuses. Consistent with our studies using sheep, intra-amniotic injection of lipopolysaccharide in wild-type mice induces large increases in surfactant protein gene expression in the preterm lungs. Demonstration of this same effect in the GR knockout mice would demonstrate this effect is independent of GR signaling.

The possibility exists that there are previously unknown mechanisms of stimulating surfactant production by the preterm lungs, which might be exploited as novel therapies for preventing respiratory distress syndrome in preterm infants. Elucidation of the effects of inflammation on the fetal lungs and other organs will allow more refined approaches to care of preterm infants exposed to inflammation *in utero*.

Moss TJ, Knox CL, Kallapur SG, Nitsos I, Theodoropoulos C, Newnham JP, Ikegami M, Jobe AH. (2008) Experimental amniotic fluid infection in sheep: Effects of Ureaplasma parvum serovars 3 and 6 on preterm or term fetal sheep. *American Journal of Obstetrics and Gynecology*. **198(1):** 122.e121-122.e128.

Moss TJM, Newnham JP, Willett KE, Kramer BW, Jobe AH, Ikegami M. (2002a) Early gestational intra-amniotic endotoxin: Lung function, surfactant, and morphometry. *American Journal of Respiratory and Critical Care Medicine* **165(6):** 805-811.

Moss TJM, Nitsos I, Kramer BW, Ikegami M, Newnham JP, Jobe AH. (2002b) Intra-amniotic endotoxin induces lung maturation by direct effects on the developing respiratory tract in preterm sheep. *American Journal of Obstetrics and Gynecology* **187(4):** 1059-1065.

Nitsos I, Moss TJM, Cock ML, Harding R, Newnham JP. (2002) Fetal responses to intra-amniotic endotoxin in sheep. *Journal of the Society for Gynecologic Investigation*. **9(2):** 80-85.