Breathing for two: maternal asthma and lung development in the fetus

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The health of the mother during pregnancy has consequences for the offspring in both the short and longer term. Asthma is a common chronic respiratory disease that affects 4-12% of pregnant women globally and is associated with greater risk of pregnancy complications, such as preeclampsia, preterm delivery and fetal growth retardation. Maternal asthma has also been linked to respiratory disorders in the neonate and childhood asthma (Mendola et al, 2014; Lui et al, 2018).

Professor Clifton and colleagues in Australia have developed a sheep model of maternal allergic asthma to examine the consequences for fetal growth and development (Clifton et al, 2016). Ewes were sensitized to house dust mite (HDM) allergens before conception and subsequently exposed to HDM allergens in airway challenges throughout gestation. The respiratory system of HDM-exposed ewes showed pathophysiological changes resembling human asthma, including blood and lung eosinophil accumulation, thickening of airway smooth muscle, and increased lung resistance in response to HDM challenge. In the fetuses during late gestation, body weight, expressed relative to maternal body weight, and pulmonary abundance of surfactant protein-B mRNA, were decreased.

In this issue, the team present their latest findings on the development of the fetal lungs and immune system in the sheep model of maternal allergic asthma (Wooldridge et al, 2019). The density of type II pneumocytes, the alveolar cells that synthesize and secrete surfactant, in fetuses of HDM-exposed ewes was reduced by 30%. Furthermore, the proportion of CD44+ lymphocytes present in the fetal thymus increased more than 3-fold, indicating activation of an immune response *in utero*. The authors propose that these changes, if persistent, may predispose the offspring to respiratory and allergic diseases in postnatal life. Future studies will no doubt focus on longer term health outcomes in the neonate and adult offspring of HDM-exposed ewes. In particular, it will be interesting to discover whether the impaired capacity for surfactant production in the fetal lungs affects lung compliance and respiratory function at birth. The timing of the stages of lung maturation is similar in ovine and human fetuses which makes the sheep a relevant species to model the effects of maternal allergic asthma on lung development *in utero*. Unlike clinical studies, these experiments can also differentiate between the effects of maternal asthma and those of medications used to treat the condition.

The mechanisms responsible for mediating the effects of maternal allergic asthma on fetal growth and development are unclear and warrant further investigation. Wooldridge et al (2019) found no evidence of HDM antibodies in the fetal circulation or an inflammatory response in the fetal lungs or amniotic fluid. Other indicators of immune function in the ovine fetus remained unchanged, including the Th1/Th2 balance. In pregnancies complicated by maternal asthma, placental development may be modified by chronic inflammation and hypoxic episodes, and in turn, impact the developing conceptus. Changes in placental growth and vascular responsiveness, and expression of genes involved in placental metabolism, inflammation, oxidative stress and glucocorticoid bioavailability, have been reported in clinical studies of maternal asthma, in a manner often dependent on the sex of the offspring (Meakin et al, 2017). Placental morphology was altered in the sheep model of maternal allergic asthma although the gross anatomy and ultrastructure of the ovine placenta is notably different to that of the human.

Glucocorticoids are well-known to promote type II pneumocyte differentiation and surfactant production before birth, especially near term when concentrations rise in the fetal circulation. No difference in plasma cortisol concentration was observed, however, between the offspring of HDM-exposed and control ewes, and concentrations were relatively low in both groups, indicating that the fetuses were not yet in the final stages of gestation. Wooldridge et al (2019) suggest that maternal allergic asthma delays maturation of the fetal lungs, albeit independent of fetal cortisol, and propose that future studies examine the potential use of antenatal glucocorticoids to improve lung structure and function affected by maternal allergic asthma.

Epigenetic modifications have been reported in blood cells at birth and at one year of age in children born to mothers with asthma (DeVries & Vercelli, 2017). Several differentially methylated regions dependent on maternal asthma status were identified which may influence immune function in later life, including genes in pro-inflammatory and immunoregulatory pathways. For example, in independent birth cohorts, hypermethylation of SMAD3 in cord blood mononuclear cells was observed in infants of asthmatic mothers who subsequently developed asthma. SMAD3 is a transcription factor involved in tumour growth factor (TGF) signalling, and is therefore important for differentiation of both immune T-cells and type II pneumocytes and surfactant production. The extent to which changes in SMAD3 and TGF signalling, via epigenetic mechanisms, contribute to the fetal sheep phenotype remains to be established.

Collectively, findings from clinical studies and animal models highlight the importance of asthma control during pregnancy for normal growth and maturation of the offspring, and respiratory and immune function in later life. Management of asthma in women of reproductive age may be equally important as the adverse consequences may arise at the time of conception. The nature of the therapeutic approach may depend on the sex of the offspring: asthmatic women pregnant with a female fetus present a more severe inflammatory condition and impaired fetal growth, which can be corrected by inhaled glucocorticoid treatment, compared to those carrying a male fetus (Murphy et al, 2003). Pregnancy can alter the symptoms of asthma and, ironically, levels of non-compliance with asthma treatment increases during pregnancy in the mistaken belief that the medication may harm the unborn child. Understanding the processes by which maternal asthma modifies development *in utero* will be essential to inform public health campaigns and the design of interventions to prevent neonatal respiratory disorders and combat the prevalence of asthma which may have origins in early life.

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