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

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8 The health of the mother during pregnancy has consequences for the offspring in both the 9 short and longer term. Asthma is a common chronic respiratory disease that affects 4-12% 10 of pregnant women globally and is associated with greater risk of pregnancy complications, 11 such as preeclampsia, preterm delivery and fetal growth retardation. Maternal asthma has 12 also been linked to respiratory disorders in the neonate and childhood asthma (Mendola et 13 al, 2014; Lui et al, 2018).

14 Professor Clifton and colleagues in Australia have developed a sheep model of maternal 15 allergic asthma to examine the consequences for fetal growth and development (Clifton et 16 al, 2016). Ewes were sensitized to house dust mite (HDM) allergens before conception and 17 subsequently exposed to HDM allergens in airway challenges throughout gestation. The 18 respiratory system of HDM-exposed ewes showed pathophysiological changes resembling 19 human asthma, including blood and lung eosinophil accumulation, thickening of airway 20 smooth muscle, and increased lung resistance in response to HDM challenge. In the fetuses 21 during late gestation, body weight, expressed relative to maternal body weight, and 22 pulmonary abundance of surfactant protein-B mRNA, were decreased.

23 In this issue, the team present their latest findings on the development of the fetal lungs and 24 immune system in the sheep model of maternal allergic asthma (Wooldridge et al, 2019). 25 The density of type II pneumocytes, the alveolar cells that synthesize and secrete surfactant, 26 in fetuses of HDM-exposed ewes was reduced by 30%. Furthermore, the proportion of 27 CD44+ lymphocytes present in the fetal thymus increased more than 3-fold, indicating 28 activation of an immune response in utero. The authors propose that these changes, if 29 persistent, may predispose the offspring to respiratory and allergic diseases in postnatal life. 30 Future studies will no doubt focus on longer term health outcomes in the neonate and adult 31 offspring of HDM-exposed ewes. In particular, it will be interesting to discover whether the 32 impaired capacity for surfactant production in the fetal lungs affects lung compliance and 33 respiratory function at birth. The timing of the stages of lung maturation is similar in ovine 34 and human fetuses which makes the sheep a relevant species to model the effects of 35 maternal allergic asthma on lung development in utero. Unlike clinical studies, these 36 experiments can also differentiate between the effects of maternal asthma and those of 37 medications used to treat the condition.

38 The mechanisms responsible for mediating the effects of maternal allergic asthma on fetal 39 growth and development are unclear and warrant further investigation. Wooldridge et al 40 (2019) found no evidence of HDM antibodies in the fetal circulation or an inflammatory 41 response in the fetal lungs or amniotic fluid. Other indicators of immune function in the 42 ovine fetus remained unchanged, including the Th1/Th2 balance. In pregnancies 43 complicated by maternal asthma, placental development may be modified by chronic 44 inflammation and hypoxic episodes, and in turn, impact the developing conceptus. Changes 45 in placental growth and vascular responsiveness, and expression of genes involved in 46 placental metabolism, inflammation, oxidative stress and glucocorticoid bioavailability, have 47 been reported in clinical studies of maternal asthma, in a manner often dependent on the 48 sex of the offspring (Meakin et al, 2017). Placental morphology was altered in the sheep 49 model of maternal allergic asthma although the gross anatomy and ultrastructure of the 50 ovine placenta is notably different to that of the human.

51 Glucocorticoids are well-known to promote type II pneumocyte differentiation and 52 surfactant production before birth, especially near term when concentrations rise in the 53 fetal circulation. No difference in plasma cortisol concentration was observed, however, 54 between the offspring of HDM-exposed and control ewes, and concentrations were 55 relatively low in both groups, indicating that the fetuses were not yet in the final stages of 56 gestation. Wooldridge et al (2019) suggest that maternal allergic asthma delays maturation 57 of the fetal lungs, albeit independent of fetal cortisol, and propose that future studies 58 examine the potential use of antenatal glucocorticoids to improve lung structure and 59 function affected by maternal allergic asthma.

60 Epigenetic modifications have been reported in blood cells at birth and at one year of age in 61 children born to mothers with asthma (DeVries & Vercelli, 2017). Several differentially 62 methylated regions dependent on maternal asthma status were identified which may 63 influence immune function in later life, including genes in pro-inflammatory and 64 immunoregulatory pathways. For example, in independent birth cohorts, hypermethylation 65 of SMAD3 in cord blood mononuclear cells was observed in infants of asthmatic mothers 66 who subsequently developed asthma. SMAD3 is a transcription factor involved in tumour 67 growth factor (TGF) signalling, and is therefore important for differentiation of both immune 68 T-cells and type II pneumocytes and surfactant production. The extent to which changes in 69 SMAD3 and TGF signalling, via epigenetic mechanisms, contribute to the fetal sheep 70 phenotype remains to be established.

71 Collectively, findings from clinical studies and animal models highlight the importance of 72 asthma control during pregnancy for normal growth and maturation of the offspring, and 73 respiratory and immune function in later life. Management of asthma in women of 74 reproductive age may be equally important as the adverse consequences may arise at the 75 time of conception. The nature of the therapeutic approach may depend on the sex of the 76 offspring: asthmatic women pregnant with a female fetus present a more severe 77 inflammatory condition and impaired fetal growth, which can be corrected by inhaled 78 glucocorticoid treatment, compared to those carrying a male fetus (Murphy et al, 2003). 79 Pregnancy can alter the symptoms of asthma and, ironically, levels of non-compliance with 80 asthma treatment increases during pregnancy in the mistaken belief that the medication 81 may harm the unborn child. Understanding the processes by which maternal asthma 82 modifies development in utero will be essential to inform public health campaigns and the 83 design of interventions to prevent neonatal respiratory disorders and combat the prevalence 84 of asthma which may have origins in early life.

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