## Midgestation intrafetal cortisol infusion in sheep increases lung surfactant protein mRNA, but not to the same degree as the normal prepartum surge in cortisol

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Pulmonary surfactant is a lipid-protein complex secreted into the liquid lining of the lung. It is essential to decrease the surface tension at the air-liquid interface, preparing the fetus for the transition to extrauterine life and air breathing. Maturation of the pulmonary surfactant system occurs late in gestation and is under control of endogenous glucocorticoids. In Australia, approximately 8% of the 280,000 annual births occur preterm which is defined as prior to 37 weeks gestation (term, 40wk). Preterm infants are often born before the lungs have completed development *in utero*. Currently, glucocorticoid administration to women at risk of preterm birth is the most common pharmacological manipulation of fetal lung and surfactant maturation reducing the prevalence of respiratory distress syndrome in preterm infants. We hypothesized that intrafetal intravenous cortisol infusion from 109-116d gestation (prior to the endogenous prepartum cortisol surge), will act functionally to accelerate surfactant protein mRNA expression to similar levels present close to term within the fetal sheep lung.

Fetal lung tissue was obtained from previous sheep cohort studies, in which vascular catheters were implanted in ewes and fetuses after intravenous injection of sodium thiopentone (1.25 g). Anaesthesia was maintained with 2.5-4% halothane inhalation in oxygen. Ewes were randomly assigned to either a saline (n=6) or cortisol (n=4) infused group. Cortisol (2-2.5mg/24h) or saline were infused into fetal sheep for a 7d period from 109-116d gestation. An older fetal cohort (n=6) received saline infusion from 130-140d gestation. The relative abundance of SP-A, -B, -C and -D mRNA transcripts in fetal lung samples was measured by qRT-PCR. Data were analyzed by one-way ANOVA followed by Tukeys *post hoc* tests and $P<0.05$ was considered significant.

Mean gestational arterial $PO_2$, $PCO_2$, pH, $O_2$ saturation and haemoglobin concentration were not significantly different as a result of cortisol infusion or increasing gestational age. There was a significant increase in fetal weight, crown-rump length and lung weight with increasing gestation. However, intrafetal cortisol infusion did not affect fetal weight, crown-rump length, abdominal circumference, lung weight or relative lung weight to body weight ratio when compared with their respective age-matched controls. Lung tissue SP-A and -B but not SP-C and -D mRNA expression were significantly increased from 116 to 140d gestation. Direct intrafetal cortisol infusion significantly increased SP-C but not SP-A, -B or -D mRNA expression compared to those at 140d gestation.

Across gestation SP-A and -B mRNA transcripts were increased in preparation for entering the air breathing environment at birth, however, SP-C and -D mRNA appear to be expressed relatively constantly over the latter stages of gestation. The inability of direct intrafetal cortisol infusion to significantly increase SP-A, and -B or -D mRNA concentrations relative to those observed close to term may indicate that at 116d gestation in the fetal sheep lung there is limited capacity of the pulmonary surfactant system to respond, possibly due to insufficient or immature type II alveolar epithelial cells or reduced glucocorticoid tissue availability. These factors may contribute to the inability of some preterm infants to respond to glucocorticoid administration as a means of stimulating surfactant protein expression and preventing respiratory distress syndrome following preterm birth.