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The impact of fetal growth and sex on placental-specific cytochrome P450 isoenzyme activity

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Introduction: Impaired placental function impacts fetal growth and development, which can then initiate further placental adaptations in an attempt to rescue fetal outcomes. This feto-placental crosstalk remains poorly understood, especially when considering cytochrome-P450 (CYP) metabolism of exogenous chemicals including drugs that may be administered in complicated pregnancies, given the activity of placental-specific CYPs remains uncharacterised. Herein, we have validated an assay to quantify placental CYP activity and determined whether fetal outcomes are associated with altered CYP activity in a sheep model of fetal growth restriction (FGR).

Methods: Non-pregnant Merino ewes were anesthetised (induction: ketamine 7 mg/kg IV and diazepam 0.3 mg/kg IV; maintenance: isoflurane 1.5 – 2% in oxygen) and underwent carunclectomy surgery to induce FGR, as well as fetal surgery at 112d gestation to collect blood gas data. Isolated microsomes from control (female n=9; male n=11) and FGR (female n=9; male n=6) placentae (140d gestation) were incubated with CYP-specific probe drugs. CYP activity was quantified using liquid chromatography-tandem mass spectrometry (LC-MS/MS) on Sciex Triple Quad 4500 LC-MS/MS system.

Results: There was no impact of FGR or fetal sex on CYP1A2, CYP2C8, or CYP2D6 activity. Irrespective of FGR, CYP1A2 activity was positively associated with fetal weight and mean gestation fetal PO_2, but negatively associated with relative brain weight in males only; no relationships were observed in females.

Conclusion: Comparable CYP activity in the presence and absence of FGR indicates placental drug metabolism may be more resilient to changes in either the maternal or fetal environments. However, the observed male-specific associations with characteristic FGR markers and CYP1A2 activity supports growing evidence showing placentae of smaller males are unable to appropriately adapt to changes in the maternal and/or fetal environments.