Sex-specific placental IGF-system adaptations to maternal exercise in growth restricted mothers

Y.T.M. Mangwiro,[1,2] J.S.M. Cuffe,[3,4] J.F. Briffa,[2] D. Mahizir,[2] K. Anevska,[1,2] T. Romano,[1] K.M. Moritz[3] and M.E. Wlodek,[2] [1]La Trobe University, Bundoora, VIC 3083, Australia, [2]The University of Melbourne, Parkville, VIC 3052, Australia, [3]The University of Queensland, St. Lucia, QLD 4072, Australia and [4]Griffith University, Southport, QLD 4222, Australia.

The insulin-like growth factor (IGF) system is central to the growth of the fetal-placental unit by controlling placental substrate capacity in response to nutrient availability as well as oxygen and hormonal signalling. Placental expression of growth factors (IGF-1 and IGF-2) as well as their receptors (IGF-1R and IGF-2R) and binding proteins (IGFBPs) are pivotal to the optimal function of this system. Dysregulation of the placental IGF-system has been strongly linked to fetal growth disorders, including intrauterine growth restriction. However, no research to date has investigated if these changes in the placental IGF-system following growth restricted are observed in placenta associated with the next generation (F2). Both growth restriction and exercise are known to alter fetal-placental growth pathways. Therefore, we aimed to investigate the impact of maternal growth restriction and endurance exercise training on the F2 placental IGF system.

Uteroplacental insufficiency was induced by bilateral uterine vessel ligation (Restricted) or sham (Control) surgery on E18 in anaesthetized Wistar-Kyoto rats (4% isoflurane and 650ml.min-1 oxygen flow, reduced to 3.2% isoflurane and 250ml.min-1 oxygen flow when suturing). Female F1 Control and Restricted offspring were Sedentary or Exercised on a treadmill 4 weeks prior to mating and throughout pregnancy (Exercise), or exercised only during pregnancy (PregEx). On E20, pregnant rats were anaesthetized with an intraperitoneal injection (30mg.kg-1 Xylazil and 100mg.kg-1 Ketamine). F2 fetal plasma was collected and pooled in each litter. Placentae were excised, weighed and labyrinth tissues were collected. IGF1, IGF2, IGF-1R, IGF-2R gene and protein expression were analysed by qPCR and Western blotting respectively. Fetal IGF1 plasma was analysed using an IGF1 ELISA. Fetal sex was confirmed using qPCR (SRY).

Exercise increased F2 fetal weight, but not placental weight compared to Sedentary. Maternal growth restriction increased placental efficiency in males from Sedentary mothers. Additionally, in Control mothers both exercises increased placental efficiency in males. However, in females, PregEx increased placental efficiency regardless of maternal birth weight. Maternal growth restriction reduced F2 placental *Igf-1r* and *Igf2* (Exercise only) mRNA abundance, and increased *Igf-2r* mRNA abundance in males. Conversely, PregEx in Restricted mothers reduced placental *Igf-2r* and increased *Igf-1r* mRNA abundance in females. In Restricted mothers who were Sedentary, placental IGF2 protein expression was increased in males, but not females. Exercise reduced placental *Igf2* mRNA abundance in males but increased *Igf-2r* in both males and females (Restricted mothers only), whereas PregEx reduced *Igf2* mRNA abundance in females. PregEx increased *Igf-2r* mRNA abundance (Control mothers only). Exercise increased IGF1 and IGF2 protein expression in males and IGF2 protein expression in female placentae, irrespective of birth weight. Exercise in Control mothers increased fetal IGF1 plasma concentrations. Whereas, PregEx increased IGF1 and IGF-1R protein expression in both male and female associated placentae.

Maternal growth restriction independently disrupts the placental IGF-system in the F2 generation in a sex-specific manner. Exercise initiated before and continued during pregnancy improved IGF protein expression in males, which may impact on fetal development regardless of maternal birth weight. Whereas, females were more responsive to Exercise initiated during pregnancy. This data highlights the sex-specific impact of the timing of maternal exercise initiation on placental and fetal development, which may have long-term offspring health consequences. However, more research is required to investigate the impact these alterations in the placental IGF-system have on offspring health.