The impact of exercise and high-fat feeding in growth restricted females on the placental IGF-system and nephron number in male fetuses

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The insulin-like growth factor (IGF) system is central to fetal and placental growth pathways 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) is pivotal to the optimal function of this system. Dysregulation of these growth factors have been strongly linked to fetal growth disorders, including intrauterine growth restriction. These placental growth factors have also been implicated in regulating fetal tissue growth and development, including kidney development and nephron number, which may be compromised with altered nutrient and maternal lifestyle factors. Both growth restriction and obesity are known to alter fetal organ development and placental growth pathways, therefore we aimed to investigate the impact that a high-fat diet (HFD) and endurance exercise training has on the placental IGF system and kidney development in male fetuses of growth restricted mothers.

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 offspring were fed a Chow or HFD (23% fat) from 5 weeks of age. Rats were Sedentary or Exercised on a treadmill from 4 weeks before mating and throughout pregnancy (Exercise), or exercised only during pregnancy (PregEx). On E20, pregnant rats were anaesthetized with an intraperitoneal injection (30mg/kg Xylazil and 100mg/kg Ketamine). F2 fetuses and placental labyrinth tissues were collected and weighed. IGF1, IGF2, IGF-1R, IGF-2R and IGFBP3 expression were analysed by qPCR. Male fetal nephron number was quantified using unbiased stereology. Fetal sex was confirmed using qPCR (SRY).

HFD increased Control and Restricted maternal body and dorsal fat weights. Placentae from male fetuses of Sedentary Restricted mothers had a reduction in IGF1 (-42%), IGF-1R (-28%) and IGF-2R (-22%) mRNA regardless of maternal diet. Both Exercise and PregEx in Chow-fed Restricted mothers reduced placental IGF2 (-35%), whereas in Control Chow-fed mothers IGFBP3 was reduced (-54%) compared to their Sedentary counterparts. Exercise in Chow-fed mother's increased male fetal weight irrespective of maternal birth weight. Exercise and PregEx in Restricted mothers prevented the placental mRNA reductions observed in the Sedentary group. PregEx increased IGFBP3 expression in placentae from Control Chow-fed mothers (+99%) compared to Sedentary. In Sedentary dams, nephron number was reduced in Restricted Chow-fed and HFD mothers (-30%), and was reduced in Control HFD mothers. Exercise, but not PregEx, in Control (+22%) and Restricted HFD (+50%) mothers increased nephron number compared to Sedentary. Exercise (-25%) and PregEx (-30%) reduced male nephron number in Control Chow-fed mothers.

Maternal growth restriction and a HFD independently disrupt the placental IGF system, which may contribute to the impaired kidney development in male fetuses, despite no changes in fetal or placental weight. Exercise restores placental growth factor gene expression, which may impact on fetal development regardless of maternal birth weight and diet. Importantly, exercise initiated prior to and continued during pregnancy restored the fetal nephron deficit if the mother consumed a HFD, which may be due to the normalisation of the placental IGF system. Despite normalisation of the placental IGF system in Control Chow-fed mothers, both Exercise and PregEx reduced fetal nephron number with the postnatal consequences requiring further long-term investigation. This data highlights the placental and fetal benefits of exercise, however more research is required to investigate the impact on offspring health.