Maternal selenium deficiency in mice alters placental function, reduces fetal glucose concentrations and impairs fetal growth

P. Hofstee, L. Bartho, D.R. McKeating, O.J. Holland, J.J. Vanderlelie, A.V. Perkins and J.S.M. Cuffe, Griffith University, Gold Coast, Southport, QLD 4222, Australia.

Introduction: Previous studies have demonstrated that low selenium (Se) status is implicated in several pregnancy complications including preeclampsia and gestational diabetes mellitus (GDM) due to impairment of antioxidant capacity and mitochondrial function. Maternal selenium concentrations also progressively decline during pregnancy and are further reduced by conditions including obesity. This highlights an important role for this micronutrient during pregnancy, however the effect of Se deficiency during pregnancy on fetal development and maternal and offspring physiology has not been investigated. This study aims to investigate the impact of selenium deficiency during pregnancy on antioxidant capacity and mitochondrial function of maternal and fetal tissues, as well as alterations in fetal growth and placental development. This study will also investigate physiological outcomes in offspring focusing on cardiovascular, metabolic and renal systems.

Methods: 42 female mice and 8 male C57b16 mice which were obtained from the Animal Resources Centre (ARC, WA, Australia), housed in accordance to the Australian Code of Practice for Care and Use of Animals for Scientific Purpose, approved by Griffith University Animal Ethics Committee (MSC/01/16/AEC). Female mice were assigned to a normal selenium (NS) or low selenium (LS) diet for four weeks prior to mating. Pregnant mice were divided into 2 cohorts. In cohort 1, pregnant mice were euthanized by cervical dislocation at embryonic day 18.5 for placental collection and assessment of maternal/fetal glucose concentrations. Placental tissues were collected for analysis of mitochondrial respiration (Oxygraph-2k) or snap frozen for subsequent analysis. Placental selenium concentrations were measured using ICP-MS. Enzymatic activity of selenoproteins thioredoxin reductase (TrxR) and glutathione peroxidase (GPx) were assessed by colorimetric assay and gene expression of SOD1, SOD2, TrxR1, TrxR2, GPx1 and GPx3 were quantified using qPCR. In cohort 2, pregnant mice gave birth naturally and offspring physiology was measured at multiple points of life. Measurements of renal function, glucose tolerance and exercise behaviour were monitored throughout. At 6 months of life, animals were euthanized by cervical dislocation for collection of fetal tissues with mitochondrial function measured in cardiac tissue.

Results: Maternal selenium deficiency did not affect maternal weight gain or blood glucose concentration prior to or during pregnancy. At E18.5, fetal body weight, blood glucose concentration and kidney and heart weights were all significantly decreased in both male and female fetuses exposed to the LS diet during pregnancy ($P<0.0001$). Male to female fetal ratio was significantly lower in the LS group ($P<0.05$) and placental to body weight ratio was increased in both sexes ($P<0.01$). Placental expression of SOD1 and SOD2 was reduced by LS ($P<0.05$) while TrxR and GPx mRNA expression and activity were unaffected. Placental dimensions, selenium concentrations and mitochondrial function were not affected in either sex. Male exposed to LS diet during pregnancy gained significantly less weight to post-natal day 30 ($P<0.0001$) and both sexes had significantly reduced blood glucose ($P<001$). As insufficient animals have been analysed through to 6 months of life, no other significant changes in physiological characteristics have yet been demonstrated.

Conclusion: Selenium deficiently is likely to be common within certain Australian populations. This research demonstrates the importance of selenium to fetal growth and glucose homeostasis, with offspring metabolic health being affected by maternal selenium status. We are yet to fully characterize renal and cardiovascular systems although preliminary data suggests that these systems may be likewise impaired. Currently, our understanding of the mechanisms involved remain rudimentary, however future studies will characterize pathways with the long term goal of identifying pathways that can be targeted with treatment options.