Metabolic and cardiorenal adaptations to pregnancy in females born small on a high fat diet and the benefits of endurance exercise training

D. Mahizir,[1] K. Anevska,[1,2] A.J. Jefferies,[1] G.D. Wadley,[1,3] K.M. Moritz[4] and M.E. Wlodek,[1] [1]Department of Physiology,The University of Melbourne, Parkville, VIC 3010, Australia, [2]Department of Physiology, Anatomy and Microbiology, La Trobe University, Bundoora, VIC 3083, Australia, [3]Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, Deakin University, Burwood, VIC 3125, Victoria, Australia and [4]School of Biomedical Sciences, University of Queensland, St Lucia, QLD 4067, Australia.

Intrauterine growth restriction programs adult metabolic and cardiorenal diseases, which are exacerbated with "second hits" such as pregnancy and obesity in females born small. Importantly, exercise is reported to have a positive effect in those born small. This study determined if a high fat diet (HFD) exacerbates the known adverse metabolic and cardiorenal adaptations to pregnancy in rats born small and whether exercise before and during pregnancy is more beneficial in preventing these complications than exercise during pregnancy alone.

Uteroplacental insufficiency resulting in growth restriction was induced by bilateral uterine vessel ligation (Restricted) or sham (Control) surgery on embryonic day 18 (E18) in Wistar-Kyoto rats (4% isoflurane and 650ml.min^{-1} oxygen flow, reduced to 3.2% isoflurane and 250ml.min^{-1} when suturing). Female offspring consumed a Chow or HFD (23% fat) from 5 weeks and were mated at 20 weeks. Female rats were exercised on treadmills for 4 weeks before pregnancy and throughout pregnancy or during the last two thirds of pregnancy only. Systolic blood pressure was measured by tail cuff and non-fasted glucose tolerance test was performed at E18. At E19, rats were individually placed in a metabolic cage to collect urine and plasma was taken by tail vein to calculate estimated glomerular filtration rate (eGFR). At E20, rats were anaesthetized with intraperitoneal injection of Ketamine (100mg/kg) and Ilium Xylazil-20 (30mg/kg) and plasma, pancreas and skeletal muscle were collected.

Control and Restricted rats exposed to a HFD were significantly heavier with higher plasma leptin concentrations compared to Chow-fed rats irrespective of exercise interventions. HFD exacerbated the pre-existing glucose intolerance in Restricted females (+18%; $p<0.05$) and importantly exercise before and during pregnancy prevented the development and exacerbation of glucose intolerance ($p<0.05$). Control and Restricted females on a HFD who exercised before and during pregnancy had increased pancreatic β-cell mass (+36%; $p<0.05$). No differences in skeletal muscle mitochondrial biogenesis markers (peroxisome proliferator-activated receptor gamma coactivator 1-α and citrate synthase activity) were detected across the groups. Metabolic dysfunction was not impacted by exercise in pregnancy alone.

No changes in pre-pregnancy systolic blood pressure were observed in all experimental groups. Restricted Chow-fed rats, and both Control and Restricted females on a HFD had an adverse cardiovascular adaptation to pregnancy with a greater reduction in systolic blood pressure during late gestation ($p<0.05$). Importantly, both exercise interventions prevented the adverse cardiovascular adaptation in these rats ($p<0.05$). Sedentary Control females on a HFD had adverse renal function (+50% eGFR; $p<0.05$) and this was not affected by exercise. Compared to Control, Restricted females that remained Sedentary had adverse renal function (+56% eGFR; $p<0.05$), which was not altered by HFD but was prevented by exercise.

In summary, pregnant females born small are at a greater risk of glucose intolerance when exposed to a HFD and this was prevented by the lifestyle intervention of exercise, potentially due to improved β-cell mass. This study also suggests that females born small have adverse cardiorenal adaptations to pregnancy. Although cardiorenal dysfunction was prevented by exercise prior to and during pregnancy and exercise during pregnancy alone, only exercise initiated before conception and continued during pregnancy prevented metabolic dysfunction.