Maternal stress during pregnancy alters placental development and glucose transporter expression

M.E. Wlodek,[1] S.S. Hosseini,[1] K.M. Moritz,[3] J.F. Briffa,[1] D. Mahizir,[1] K. Anevska[1,2] and J.S.M. Cuffe,[3]
[1]Department of Physiology, The University of Melbourne, Parkville, VIC 3010, Australia, [2]Department of Physiology, Anatomy and Microbiology, La Trobe University, VIC 3083, Australia and [3]School of Biomedical Sciences, University of Queensland, St. Lucia, QLD 4067, Australia.

Introduction: Growth restricted individuals have increased risk developing metabolic diseases, with males more susceptible. Interestingly, we have demonstrated that growth restricted females lose this protection and develop glucose intolerance during pregnancy. It has been identified that maternal stress during pregnancy adversely impacts fetal development. We have reported that maternal stress during pregnancy and maternal growth restriction impacts offspring metabolic health independently. As the placenta mediates offspring disease outcomes, this study investigated the effects of maternal stress and maternal growth restriction on placental development and glucose transporter expression.

Methods: Uteroplacental insufficiency was induced by bilateral uterine vessel ligation (Restricted) or sham (Control) surgery in anaesthetized (4% isoflurane and 650ml.min-1 oxygen flow, reduced to 3.2% isoflurane and 250ml.min-1 oxygen flow when suturing) Wistar-Kyoto rats on embryonic day (E) 18 (term=22 days). F1 Control and Restricted females were mated with a healthy male at 4 months of age and were randomly allocated to an Unstressed or Stressed pregnancy. For the Stressed groups, physiological stressors (metabolic cage measurements, tail cuff blood pressure, glucose tolerance test and indirect open-circuit calorimetry) were introduced from mid gestation (E8). On E20, pregnant rats were anaesthetized with an intraperitoneal injection of Xylazil (30mg/kg) and Ketamine (100mg/kg) and the uterus exposed. Fetuses and placentae were collected and weighted, with fetal sex verified using qPCR. Placental morphology was examined using stereology and placental expression of glucose transporters (Glut1 and Glut3) were performed on the labyrinth zone using qPCR. All data were analysed by two-way ANOVA.

Results: There were no changes in F2 fetal weight in either sex. Male fetuses had an increased placental efficiency (+5%) if their mother was Restricted, irrespective of maternal Stress. Junctional-to-labyrinth zone ratio reduced (-19%) in placentae of females of Restricted mothers. Female placental weights were not different, however male fetuses whose mother were exposed to Stress had reduced placental weight (-6%), irrespective of maternal birth weight. Placentae of females whose mothers were Stressed had increased junctional zone cross sectional area (+20%). Placentae of both males and females had increased Glut1 expression (+43% and +68%, respectively) if their mother was Stressed, with no changes in Glut3 expression. Maternal Stress only increased glycogen cells in female placentae (+47%), irrespective of birth weight.

Conclusion: Both maternal growth restriction and maternal stress independently influenced placental development in a sex-specific manner. Interestingly, maternal growth restriction and maternal stress exposure did not exacerbate the effects of one another. Maternal growth restriction only altered placental morphology in females. Whereas, maternal stress increased placental glucose transport in both sexes, but only resulted in increased junctional zone and glycogen stores in placentae of females. This finding suggests that female fetuses have functional adaptations that may be storing energy in order to protect them from other *in utero* insults that may occur.