Maternal glucocorticoids impair placental development, induce cellular stress and program fetal outcomes in a sex specific manner

J.S.M. Cuffe, School of Medical Science, Menzies Health Institute Queensland, Griffith University, Gold Coast Campus, Southport, QLD 4222, Australia.

The birth of a healthy child depends on the coordinated interactions of multiple maternal biological systems which act to maintain an intrauterine environment optimal for fetal growth. Numerous maternal perturbations disrupt the intrauterine environment and impair placental function, resulting in poor developmental outcomes. Studies have demonstrated that the incidence of many of our most debilitating chronic diseases is largely influenced by insults that occurred in the womb. Indeed, many human and animal studies have demonstrated that an adverse maternal environment can lead to fetal growth restriction, impaired organ development and a myriad of offspring health concerns. Of great significance, a multitude of different maternal perturbations have been shown to program an increased susceptibility to specific cardiovascular, metabolic and neurological disturbances which suggests common mechanisms may regulate outcomes.

By using a number of different animal models, I have identified a key maternal and placental adaptations that occur in response to a variety of different maternal events. The degree to which these adaptations occur depends largely on both the sex of the fetus and the timing of the insult. These sex and time dependant adaptations are strongly associated with the severity of disease outcomes in offspring, with males often being more vulnerable to programmed disease than females.

I have demonstrated that maternal glucocorticoids and placental glucocorticoid signalling are central mediators of programmed disease outcomes. Cellular stress within the placenta plays a key role in a number of pregnancy complications. In addition, it is likely to play a significant role in mediating sex specific programming of disease. In particular, the current literature supports a key role for oxidative stress as a central mediator of regulating the cellular stress response following a maternal “stress”. However, the mechanistic relationship between placental glucocorticoid signalling and the intracellular stress response is poorly understood. The current project aimed to investigate the relationship between maternal stressors, circulating glucocorticoid levels and placental oxidative stress.

Maternal exposure to dexamethasone, a synthetic glucocorticoid, had no effect on oxidative stress levels measured by DCF assay in Swan 71 trophoblasts. Similarly, maternal dexamethasone exposure in the mouse did not alter protein carbonyl levels in placental tissue, indicating no change in oxidative stress. In contrast, administration of the endogenous glucocorticoid cortisol to Swan 71 trophoblasts induced oxidative stress in a dose dependant manner. Maternal administration of corticosterone (rodent equivalent to cortisol) to pregnant mice increased oxidative stress levels in placentas of female but not male fetuses. In addition, we have evidence to suggest that glucocorticoids induce sex specific alterations in endogenous antioxidant proteins including the selenoprotein thioredoxin reductase. I am currently investigating how these antioxidant proteins might be involved in the sex specific regulation of programmed disease by using an animal model of selenium deficiency. Our current data demonstrates that selenium deficiency in mice also causes fetal growth restriction which may increase offspring risk of programmed disease

Collectively, these studies support previous research which has suggested that glucocorticoids or cellular stress might mediate programmed disease outcomes. Indeed, these two proposed mechanistic pathways are likely to be linked and together mediate programmed disease outcome.