

Maternal overnutrition during the periconceptional period and gender influences insulin signalling and glucose handling in lambs after birth

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The increased prevalence of overweight and obesity amongst Australians aged 18 years and older is reflected in an increase in the number of women who are entering pregnancy obese (Callaway, O'Callaghan & McIntyre, 2009; Ryan, 2007; LaCoursiere *et. al.*, 2005). Maternal obesity before pregnancy is associated with an increased risk of obesity and metabolic disease in the offspring (Catalano *et. al.*, 2003). How the liver responds to insulin is an important contributor to the body's ability to maintain normal glucose levels throughout life (Postic, Dentin & Girard, 2004). Little is known, however, about the impact of maternal obesity or the impact of dieting before conception on how the liver of her offspring responds to insulin in order to maintain glucose homeostasis. The present study investigated whether maternal obesity during the periconceptional period (*i.e.* before and just one week after conception) resulted in changes in the expression of insulin signalling molecules and genes that control glucose output in the liver of postnatal lambs. This study also investigated the effects of dietary restriction in overnourished and normally nourished ewes on these measures of hepatic insulin sensitivity in the offspring.

Donor ewes were randomly allocated to one of 4 treatment groups. The CC group received a control diet of 100% metabolisable energy requirements (MER) for 4 months before conception. The CR group received a diet of 100% MER for 3 months followed by a restricted diet (70% MER) for 1 month. Ewes in the HH group, which is our model of maternal periconceptional overnutrition, was overnourished (~180% MER) for 4 months. The HR group, which is our model of dietary restriction in the overnourished ewe, was overfed for 3 months followed by a restricted diet of 70% MER for 1 month. After conception, single embryos were transferred into non obese 'recipient' ewes at 6-7 days after conception. Ewes lambed normally and tissues including the liver were collected at 4 months of age for analysis.

There was a lower ($p<0.05$) abundance of insulin signalling proteins Akt2, pAkt and pFoxO1 in the HH group and this effect was ameliorated in the HR group. Interestingly, expression of the gluconeogenic enzyme PEPCK (mitochondrial form) and 11 β HSD1 mRNA was lower ($p<0.05$) in the HH group and this effect was also abolished in the HR group. In addition, expression of the cytosolic form of PEPCK mRNA was lower ($p<0.05$) in CR, HH (male lambs) and HR groups.

In conclusion, periconceptional overnutrition appears to program decreased expression of insulin signalling molecules in the liver of the offspring which could contribute to the emergence of insulin resistance in later life. In contrast, periconceptional over- and under-nutrition differentially suppress the mitochondrial and cytosolic forms of the major gluconeogenic enzyme in the liver which may protect the lamb from the consequences of poor insulin signalling in the immediate term.

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