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One carbon metabolism and complications of pregnancy

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Placental dysfunction is implicated in a range of common complications of pregnancy including gestational diabetes mellitus (GDM), preeclampsia, fetal growth restriction and preterm birth. There are several risk factors associated with the increased risk of developing such complications including changes to micronutrition or metabolic disruption. One-carbon metabolism is a central biological process that links together deficiencies in key micronutrients and pregnancy complications such as GDM and growth restriction. The micronutrients of most significant interest in relation to one-carbon metabolism include Vitamin B12, folate, methionine, Vitamin B6 and choline. Previous studies highlight that the relationship between these micronutrients, metabolic disruption in pregnancy and adverse pregnancy outcomes is highly complex. It remains unclear if deficiencies in these micronutrients are driving adverse pregnancy outcomes, if metabolic changes in pregnancy that are associated with pregnancy dysfunction are altering plasma concentrations of these micronutrients or if treatments for these conditions are reducing concentrations of such micronutrients.

My research group has undertaken a number of related animal studies to investigate the role of one-carbon micronutrients in adverse outcomes in pregnancy. We have demonstrated that exposure to a 95% reduction in vitamin B12 for four weeks, induces a diabetic-like phenotype in non-pregnant females. This was associated with disruption to most components of the one-carbon cycle in the liver with changes also identified in circulation. Furthermore, when we have directly induced hyperglycemia in pregnancy by implantation of an osmotic minipump, maternal concentrations of B12, B6, methionine and a range of one-carbon metabolites were increased. In this model, the expression of one-carbon metabolizing enzymes within placental tissue was altered. We have also demonstrated that metformin, a common anti-hyperglycemic medication, reduces plasma concentrations of range of one-carbon micronutrients and metabolites in pregnant rats. Finally, we have found that alcohol exposure around conception leads to changes in the choline cycle and its associated one-carbon metabolites. In this presentation, I will summarise the key findings from each of these studies and highlight some of the new insights developed from these projects regarding the importance of these biochemical pathways in relation to adverse pregnancy outcomes.