

Breaking the cycle of intergenerational obesity

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There is now a large body of evidence describing the significant risk of obesity and metabolic complications in the children of mothers who were over-weight or obese during pregnancy (Zou *et al.*, 2016). As rates of maternal obesity increase across many populations, an urgent need has arisen for clinically applicable strategies to help prevent obesity from being perpetuated across generations. However, despite a number of trials of various antioxidant and other compounds in animal models, few interventions hold significant translational promise.

The paper by Zou *et al.*, in this issue of *The Journal of Physiology*, demonstrates using a high-fat maternal diet mouse model that supplementation with resveratrol during pregnancy improves insulin sensitivity and reduces obesity in high-fat fed offspring (Zou *et al.*, 2016). These striking findings suggest that resveratrol supplementation to obese mothers has beneficial effects in the offspring, at least in part by altering the composition of offspring adipose tissue from white to beige. The metabolic benefits of such a transition are well established, leading to enhanced ability to dissipate excess energy as heat rather than storing it as lipid. Not only were molecular endpoints and the composition of adipocytes in offspring demonstrably changed when resveratrol was added as a maternal supplement, but there were also improvements in important downstream clinical endpoints. In particular, the offspring whose mothers had received resveratrol supplementation during pregnancy had reduced weight gain and improved insulin sensitivity in adulthood even when fed a high-fat diet.

As with other polyphenol dietary supplements that have been suggested as translatable interventions, there are a number of considerations that must be carefully evaluated prior to a trial in human pregnancy. The primary concern with any supplement or pharmacological agent in pregnancy is a full evaluation for any

possibility of teratogenicity or adverse impact on fetal development and immediate pregnancy outcome. Reports have suggested that resveratrol may be detrimental to normal fetal adrenal development (Savchuk *et al.*, 2016), which could have potential long-term consequences for steroidogenesis in offspring. If such an effect occurs in human pregnancy then this is likely to rule out resveratrol as a beneficial intervention. The second issue relates to bioavailability in humans, both in the maternal circulation and its ability to cross the placenta. While studies suggest that resveratrol can move across the placental barrier and into cells, it is relatively insoluble in water (Balata *et al.*, 2016). This creates challenges in achieving high enough plasma concentrations of resveratrol in the mother to make it available to the fetus. If the beneficial effects of resveratrol are direct effects on the fetus, then this is an important issue. However, if the offspring effects of resveratrol are mediated via its effects on the maternal metabolic milieu, then lower plasma concentrations may still be effective. The relative contributions of these two mechanisms should be evaluated in the future, potentially by measuring transplacental resveratrol concentrations, or by direct fetal catheterization. Other considerations include efficacy within a safe and feasible dosing range. Resveratrol doses previously trialed in human subjects lie in the 20-50mg/kg/day range (Gambini *et al.*, 2013), whereas the study of Zou *et al.* used a dose of 200mg/kg/day in the rodent (which may be accounted for by relatively high metabolic rates). This raises the important question of whether the beneficial offspring effects reported by Zou *et al.* would still occur at the lower doses suitable for human consumption.

An under-reported and widely ignored aspect of the perpetuation of obesity through generations is the direct impact of maternal obesity on the social aspects of child development. A key positive feature of resveratrol supplementation in pregnancy as reported by Zou *et al.*, is that it promotes postpartum weight loss, reduces adipose tissue mass, and increases insulin sensitivity in the obese mother. The positive role-modeling from a mother whose weight and eating behaviour are within the normal range may itself be protective against offspring obesity (Thompson, 2013). This aspect is particularly important when considering the translational implications in humans, where learned aspects of eating, appetite, and exercise patterns are prominent in childhood development. Furthermore, resveratrol supplementation to obese mothers during pregnancy increases postpartum weight loss and hence is likely to reduce inter-pregnancy weight gain. Maternal resveratrol may thus be of benefit not only to the fetus of the index pregnancy but also potentially to future offspring, via a reduced likelihood of pregnancy complications associated with maternal obesity.

In future studies it will be important to address whether the beneficial effects of maternal resveratrol supplementation are limited to situations of obese pregnancy or if it would be effective in mitigating the risks of other adverse exposures during pregnancy, for example other dietary manipulations, chronic hypoxia and increased stress. There are very limited data regarding whether 'natural' dietary supplementation with resveratrol could be sufficient to ensure high enough concentrations of the bioactive compound. Furthermore, the gestational window during which resveratrol supplementation would be of benefit is not clear from available data. It will be particularly important to define the potential window of opportunity to improve offspring outcome using resveratrol if it extends beyond the pregnancy period. An ideal intervention to break the intergenerational cycle of obesity may be one that is not only effective as a maternal supplement during pregnancy but

one that could also be applied during neonatal life if the initial window of opportunity was missed. Further studies will be required to establish if resveratrol represents such an intervention.

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