

## **Legacy of excess: consequences of maternal obesity for the adult offspring**

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Developmental programming is the process whereby the environment before birth and in early neonatal life influences the structure and function of developing physiological systems with long lasting consequences for health in adult life. When the concept of developmental programming and the 'Developmental Origins of Health and Disease' was first proposed, the hypothesis focused on the effects of a low nutrient environment on offspring physiology (Barker, 2004). Epidemiological data showed that term infants born small were more likely to suffer from metabolic and cardiovascular disease in adult life, including type II diabetes, non-alcoholic fatty liver disease (NAFLD) and coronary heart disease, compared to those born of average weight. The fetus exposed to under-nutrition appears to develop a 'thrifty phenotype' which is beneficial for survival in the short term, but which predisposes the offspring to metabolic and cardiovascular dysfunction in later life.

More recently, attention has turned to the consequences of maternal over-nutrition which has become an increasing concern in the developed world. In the UK, approximately 50% of women of reproductive age are overweight or obese, and 1 in 5 women are obese during pregnancy. The effects of over-nutrition during pregnancy have been examined in a wide range of epidemiological, clinical and experimental animal studies (Glastras et al, 2018). Maternal obesity has been shown to impact the development of the placenta, early embryo and fetus with consequences for the offspring in the short and longer term. Higher incidences of both growth restriction and macrosomia are observed in babies born to obese mothers, and these infants at opposite ends of the birth weight spectrum are at greater risk of metabolic and cardiovascular dysfunction in later life. Interestingly, there are similar long term outcomes in human and animal offspring that were exposed to either maternal under- or over-nutrition before birth, both sub-optimal environments for normal growth and development.

A variety of interacting mechanisms may be involved in developmental programming by maternal obesity, including exposure to maternal metabolites and adipose-derived cytokines with epigenetic and other effects. Maternal obesity is associated with elevated systemic and tissue levels of inflammatory factors, and markers of inflammation, oxidative stress and endothelial dysfunction in the placenta. In this issue, Lomas-Soria and colleagues have examined the mechanisms that may be responsible for hepatic dysfunction and NAFLD in the offspring of a rat model of maternal obesity (Lomas-Soria et al, 2018). Rats were fed a high fat, obesogenic diet from weaning and during pregnancy and lactation. The young adult offspring were hyperinsulinaemic and hypertriglyceridaemic, and showed greater body adiposity and hepatic triglyceride content than the offspring of dams fed the control diet. More marked changes in liver enlargement, histology and fat content were observed in the male compared to female offspring. The study also provides important information on underlying molecular changes to complement the findings in the fetuses of non-human primates fed a high fat diet during pregnancy (McCurdy et al, 2009). In the fetal liver, early signs of NAFLD were characterised by increased triglyceride content, oxidative stress and activation of gluconeogenic pathways. These changes were associated with high concentrations of inflammatory cytokines in the fetal circulation. Taken together, these studies demonstrate that a maternal high fat diet influences hepatic development in the fetus with effects that persist into adulthood to increase the risk of NAFLD.

Following bioinformatic analysis of the offspring liver transcriptome, Lomas-Soria et al (2018) report a number of differentially expressed genes in response to maternal obesity. In male offspring, 1317 genes were down-regulated compared to only 24 genes in the female offspring, and 40-50 genes

were up-regulated in both sexes. Many of the genes affected were related to insulin signalling, and glucose and lipid metabolism in the liver. These findings highlight a range of new targets for future investigation. Further studies are also required to determine whether these molecular changes are responsible for, or are secondary to, the developmental programming of hepatic dysfunction.

Remarkably, only 1 common gene showed a consistent response to maternal obesity in both male and female offspring. Therefore, in pregnancies complicated by maternal obesity, there may be differences in the sensitivity of male and female offspring to the intrauterine environment and/or separate molecular pathways in the subsequent programming of hepatic dysfunction. The distinct profiles of responsive genes, and differences in hepatic phenotype observed between the sexes, also reinforce the importance of considering data from males and females separately. Sexual dimorphism is a well-recognised feature of developmental programming (Dearden et al, 2018). The mechanisms responsible for sex-dependent outcomes are unclear but differences in epigenetic processes within the placenta, hypothalamus and adipose tissue have been reported in experimental animal studies.

The study by Lomas-Soria et al (2018) contributes to our understanding of developmental programming of hepatic function by maternal obesity and raises a number of important questions: What are the mechanisms that protect the female offspring from the adverse effects of maternal obesity on hepatic structure and function? To what extent do the molecular changes observed in male offspring contribute to the 'male disadvantage' in morbidity, including NAFLD, and longevity? The alarming rates of NAFLD and type II diabetes, especially in children and adolescents, parallel the global epidemic in obesity, and this relationship may originate in early life. Further research is vital to map the effects of the intrauterine environment on metabolic function, and the molecular mechanisms responsible, over the life course of an individual and to assess the potential of intervention strategies before and after birth.

## References

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