Module 7 – Optimising health for genetic programming

Learning objectives:

At the end of this module you should be able to:

1. Describe the impact of toxins on epigenetic programming
2. Understand the role of Body Mass Index on epigenetics
3. Label key nutrients which have been found to play a role in epigenetic programming
4. Explain the impact of the preconception maternal and paternal gut microbiome on epigenetics

At conception, genetic material from the egg and sperm combine to form an embryo. The genetic make-up of this embryo not only includes traits inherited from both parents, but also carries epigenetic information that reflects their life exposures and those of generations before them. In terms of research, much emphasis has been placed on *in utero* exposures from the mother and their impact on embryonic and foetal development. Increasingly however, there is an acknowledgement that exposures prior to conception can also have a profound impact on both fertility and the health of offspring.[1]

Environmental toxins

Most of our understanding of the impact of preconception exposures on offspring health have come from studies of environmental toxins. One example is the dioxin containing herbicide, Agent Orange, that has been linked to an increased incidence of cleft palate and neural tube defects in the offspring of Vietnam veterans exposed to the toxin during the war.[2] Polychlorinated compounds, heavy metals, phthalates and pesticide exposures in both males and females have also been associated with a range of adverse reproductive and developmental outcomes including increased time to pregnancy, genital malformations (e.g. cryptorchidism), low birthweight, pre-term delivery and childhood leukemia. [2]

Alcohol

While alcohol use disorder is a highly heritable psychiatric disease, efforts to elucidate that heritability by examining genetic variation (e.g., single nucleotide polymorphisms) have been insufficient to fully account for familial risk. There has been a burgeoning interest in the role of epigenetics that may be shaping germ cells (oocytes and sperm). More recent studies suggest that alcohol exerts a cross-generational effect similar to chronic stress, and excitingly studies have begun to delineate genomic loci that are sensitive to alcohol and associated with cross-generational effects.[3]

Consequently, it seems that the goal is not just to avoid Foetal Alcohol Syndrome, but to avoid the epigenetic effects of alcohol. For example, a fascinating study of rats concluded that preconception

alcohol was associated with changes in expression and methylation profiles of stress regulatory genes in various brain areas, thereby increasing rates of anxiety in rat progeny.[4] It is interesting to note that increased anxiety in humans is often correlated with alcohol consumption.[5] Given the prevalence of alcohol exposure, and increasing rates of anxiety disorders, this is a key message for couples planning to conceive.

Dietary fat

Recent attention has been given to low-level chronic exposures that may also pose a significant risk to reproductive and offspring health. Animal studies have provided strong evidence for the role of lifestyle factors such as preconception diet, obesity and stress on the health of their offspring. In terms of diet, Ng et al.[6] found the that the female offspring of male rodents chronically fed a high-fat diet had reduced pancreatic β-cell mass, impaired insulin secretion and developed impaired glucose tolerance. Similarly, male mice who developed obesity and pre-diabetes from consuming a high fat diet were shown to produce offspring that have an increased susceptibility to diabetes through the inheritance of epigenetic changes that alter the expression of genes involved in glucose metabolism and pancreatic β-cell function.[7]

Obesity

In parallel with the global obesity epidemic, the prevalence of obesity among women of childbearing age has also increased. In 2009–2010, the National Health and Nutrition Examination Survey (NHANES) found that 56% of US women aged 20–39 were overweight or obese (body mass index (BMI) ≥ 25 kg/m^2), and in particular, 32% were obese (BMI ≥ 30.0 kg/m^2).[8] Thus, more than half of women starting their pregnancy are already overweight or obese, and most of them remain overweight or obese during their entire pregnancy. To further complicate things, women who are overweight or obese going into pregnancy are at an increased risk for developing metabolic disorders, such as gestational diabetes mellitus (GDM),[9] hypertensive disorders of pregnancy,[10] and excessive gestational weight gain (GWG).[11] More important, maternal obesity and its relevant metabolic disorders may impact offspring metabolic risk in later life.

Excessive maternal pre-pregnancy weight and GWG are consistent risk factors for offspring obesity and cardiometabolic risk.[12] [13] In the Jerusalem Perinatal Family Follow-Up Study, greater maternal pre-pregnancy BMI, independent of GWG and confounders, was significantly associated with higher offspring blood pressures, serum insulin and triglyceride concentrations, BMI, waist circumference, and lower high-density lipoprotein cholesterol. [14] Of note, the associations between maternal BMI and offspring BP, insulin, and lipids appeared to be largely mediated by offspring concurrent body size (both BMI and waist circumference). This finding emphasizes the impact that maternal adiposity may have through offspring adiposity on various predictors of subclinical and clinical disease, including diabetes mellitus and cardiovascular diseases. A large US cohort study reported that excessive maternal GWG was independently associated with a 46% increased risk of overweight or obesity in offspring at 2–5 years of age.[15] In a retrospective cohort study, excessive maternal GWG had an adverse impact on the risk of childhood overweight and abdominal adiposity.[16] Kaar et al. further reported that maternal pre-pregnancy BMI was not only associated with increased general adiposity (BMI) and abdominal adiposity (waist circumference) in offspring but visceral adipose tissue at age 10 years.[17] A recent study points to an association between maternal excess weight in pregnancy and offspring BMI increase from adolescence to adulthood.[18] Early pregnancy obesity has also been associated with an increased risk of premature death in adult offspring.[19] To further the

negative impact, maternal pre-pregnancy BMI was also associated with increased offspring insulin resistance at age 10 years and an increased risk of developing T2DM. [17] [20]

Studies of mice show that paternal obesity can also influence weight in the next generation. For example, female offspring from sperm exposed to reactive oxygen species developed glucose intolerance and accumulated more adipose tissue when compared to the offspring of control sperm, suggesting that increased oxidative stress may be one mechanism by which paternal obesity can impact foetal and offspring health.[21] Excitingly, given that studies in obese male rodents have demonstrated that diet and exercise can reverse parental epigenetic programming in offspring, it may be possible to achieve similar outcomes in obese men. [22] [23]

Undernutrition

Preconception undernutrition have been linked to a wide range of lifelong health risks. Researchers believe that much of these may be linked to a compromised immune system. The developing immune systems seems to be particularly vulnerable to preconception malnutrition. Current models of immune development depict a layered expansion of increasingly complex defences, which may be permanently altered by maternal malnutrition. One programming mechanism involves activation of the maternal hypothalamic-pituitary-adrenal axis in response to nutritional stress. Fetal or neonatal exposure to elevated stress hormones is linked in animal studies to permanent changes in neuroendocrine-immune interactions, with diverse manifestations such as an attenuated inflammatory response or reduced resistance to tumor colonization. Maternal malnutrition may also have a direct influence, as evidenced by nutrient-driven epigenetic changes to developing T regulatory cells and subsequent risk. However, early alterations to the immune system, resulting from either nutritional deficiencies or excesses, have broad relevance for immune-mediated diseases, such as asthma, and chronic inflammatory conditions like cardiovascular disease.

Evidence for the effect of preconception and periconceptional risk factors on childhood outcomes such as obesity and other non-communicable diseases in later life is growing. Issues such as maternal malnutrition need to be addressed before pregnancy, to prevent a transgenerational passage of risk of non-communicable diseases. Research suggests that women who received preconception interventions were more likely to have improved pregnancy-related and behavioural outcomes.[24]

Additionally, paternal exposure to famine or undernutrition have also been associated with a higher BMI in offspring compared with the offspring of fathers who were no exposed to famine.[25]

Optimise nutrient stores

Low pre-conception nutrient stores may also impact offspring future health. There are now data indicating that deficiency or low levels of certain micronutrients (vitamins B_6, B_{12} and D, riboflavin) is extremely prevalent in pregnant women and has lasting effects on the offspring's risk of obesity, acting through epigenetic processes.[26] [27] [28] Meta-analysis of observational studies strongly points to a role for maternal vitamin D deficiency in GDM,[29] and additional vitamin D in pregnant women with GDM has been shown to have beneficial effects on glycaemia and total and low-density lipoprotein cholesterol (LDL)-cholesterol concentrations.[30] Low zinc intake and status has also been linked with maternal glycaemia.[31] Additionally, an increasing number of publications suggest that myo-inositol may reduce insulin resistance during pregnancy.[32] [33] [34] [35]

The NIPPER study ('Nutritional Intervention Preconception and during Pregnancy to maintain health glucosE levels and offspRing health) is a multicentre trial investigating the impact of nutrition.[36] Participants have been recruited from five different ethnic groups across three different countries. Women are followed from pre-conception until their babies turn one and are asked to drink one of two randomised nutritional supplement drinks containing a mix of micronutrients and probiotics twice each day. The trial is based on the premise that certain micronutrients such as vitamin D and B vitamins can "program" the baby by switching genes on and off to influence the risk of childhood obesity and other metabolic conditions. The study also aims to collate a biobank of urine, blood and hair samples for future research. All subjects have been recruited and results should be available soon.

In addition to metabolic effects, emerging research suggests that replete preconception B vitamin status may play an epigenetic role in future tumor development, and low preconception haemoglobin and ferritin levels may increase the risk of poor fetal growth and low birth weight due to an epigenetic paradigm.[37] [38]

Furthermore, emerging evidence suggests a role for the dietary polyphenols resveratrol, genistein, epigallocatechin-3-gallate and anthocyanins in chronic disease prevention.[39] Controversy remains over how much vitamin D should be given in the lead up to conception and during pregnancy, as the fetus derives vitamin D exclusively from maternal stores, and whilst the mother may receive adequate amounts to avoid rickets, the impact of vitamin D and its metabolites on genetic signalling during pregnancy is an area of great activity and still in its early stages.[40]

Microbiome

There is now substantial evidence implicating a role for the gut microbiome in affecting a wide range of metabolic and immune-related diseases including (but not limited to) asthma, glucose metabolism, diabetes, Coeliac disease and obesity. [41] [42] Although an infant's microbiota is adaptable throughout the first three years of life, other than the impact of antibiotics and disease onset, the microbiota is relatively stable after that.[43] Infants inherit an early microbiota 'code' from both their mother and father through the eggs and sperm.[44] Emerging evidence suggests that preconception probiotics may assist epigenetic programming through balancing gut microbiota and lowering systemic inflammation, however it is recommended that microbiota-optimising dietary strategies (such as prebiotic foods) are adopted.[45]

Future interventions

Preconception might be understood as the time from the intention to conceive to actual conception, but this narrow definition ignores the fact that many pregnancies (up to 50%) are unplanned.[46] High-risk factors such as obesity and undernutrition will take months or even years to address, so in addition to working with individuals, it is essential that a heightened awareness of the importance of nutrition on epigenetics becomes better known and that population levels changes are instigated.

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