

## **Maternal microbial and metabolic influences on programming reproductive and metabolic outcomes**

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In recent decades, epidemic levels of chronic disease states including obesity, diabetes, and cardiovascular diseases, whose social and economic impacts have prompted a global investigation into their causes as well as their consequences. Though initially considered to be determined largely by genetic and lifestyle factors, this paradigm would ultimately be insufficient to explain the continued propagation of non-communicable diseases. It is now established that perturbations during critical developmental windows result in (mal)adaptations that confer long-term disease risk, rather than health. By extension, alterations in maternal physiology are implicated by this discovery, as it is the primary determinant of the fetal environment during vulnerable critical windows. In our work, we have investigated how adversity early in life impacts on reproductive and metabolic outcomes. We show that both insufficient caloric intake as well as nutrient excess impairs ovarian growth and development and results in premature ovarian aging through pathways that are defined very early in the neonatal ovary. Furthermore, experimental and clinical studies have been essential to defining the nature and extent of the influence that the mother's own metabolic status has on the developing fetus. An altered substrate and inflammatory profile is said to program the offspring, resulting in a maladapted physiology and increased disease risk. In this regard, we show that diet-induced obesity modifies maternal gut microbial communities, characterized by increased levels of the genera *Bifidobacterium* and *Akkermansia*. These shifts in gut community composition may be impacting maternal metabolism through altered production of bacterial metabolites, including short-chain fatty acids (SCFAs) impacting intestinal permeability and immune function. Maternal metabolic compromise in turn results in an adverse fetal environment that impacts on placental function and ultimately will lead to (mal) adaptations in the fetus and postnatal offspring.