Maternal Metformin Exposure in a Non-Diabetic Mouse Model Modulates Offspring Gut Microbiota and Preserves Diversity under High-Fat Diet

Da Dat Ly
Deakin University, School of Medicine, IMPACT, The Institute for Mental and Physical Health and Clinical Translation, Geelong, Australia

Trang Truong
Deakin University, School of Medicine, IMPACT, The Institute for Mental and Physical Health and Clinical Translation, Geelong, Australia

Bryony McNeill
Deakin University, School of Medicine, IMPACT, The Institute for Mental and Physical Health and Clinical Translation, Geelong, Australia

Kathryn Aston-Mourney
Deakin University, School of Medicine, IMPACT, The Institute for Mental and Physical Health and Clinical Translation, Geelong, Australia

Leni R. Rivera
Deakin University, School of Medicine, IMPACT, The Institute for Mental and Physical Health and Clinical Translation, Geelong, Australia

Abstract:

Backgrounds: Gut microbiota is associated with key metabolic indicators, including body weight, fasting plasma glucose, and HbA1c. Dysbiosis during pregnancy can impair offspring development in several aspects including gut, brain and immune system. Metformin, known to modulate gut microbiota, is widely used in pregnancy for both diabetic and non-diabetic conditions. However, its impact on gut microbiota during pregnancy remains poorly understood. This study investigates how maternal metformin treatment alters offspring gut microbiota and its implications for offspring's health in later life under the exposure to metabolic risk factors such as high fat diet.

Methods: C57BL/6J mouse model was used for its similarity to human regarding gut anatomy and microbiota. Non-diabetic dams received metformin (5g/L) or vehicle in drinking water during pregnancy. At birth, the offspring were cross-fostered to vehicle-exposed dams to ensure them only expose to metformin during pregnancy. Then male and female offspring were fed either low or high fat diet (HFD) from 8 to 29 weeks of age. At the end of study, there are 8 offspring subgroups classified by sex, vehicle/metformin exposure, low/high fat diet. Faecal samples were collected from all offspring at 5, 13 and 29 weeks of age (n = 8 per subgroup) to characterise gut microbiome composition at different taxonomic levels using full-length 16S rRNA sequencing analysed in RStudio.

Results: α diversity was similar between vehicle and metformin-exposed offspring before HFD. HFD significantly reduced a diversity in vehicle-exposed offspring but not in metformin group ($p<0.05$). The pattern was more consistently observed in female compared to male offspring. β diversity differed by metformin exposure and diet ($p<0.01$) with clearer differentiation attributed to diet factor. Metformin significantly increased Proteobacteria and short-chain fatty acid-producing genera (Lachnospiraceae NK4A136, Eisenbergiella) while reducing potentially harmful genera (Desulfovibrio, Ileibacterium) (adjusted $p<0.01$).

Conclusion: Metformin exposure during pregnancy modulated offspring gut microbiota by preserving a diversity under HFD, enriching short-chain fatty acid-producing taxa and reducing potentially harmful genera. These shifts may support metabolic resilience and health outcomes. Further studies are needed to clarify their functional mechanisms and role in pregnancy and offspring interventions.