**The direct effect of gestational metformin on offspring long-term metabolism and development.**

Metformin has been widely used to treat diabetes during pregnancy since the 1970s, offering many short-term benefits for both mother and child. However, some clinical studies suggest that prenatal exposure to metformin may increase the risk of obesity in offspring during adulthood. Given the limitations of long-term human studies, animal models are necessary to better understand these potential effects.

Aim- To assess the direct long-term effects of gestational metformin exposure on offspring using a healthy mouse model. A healthy model eliminates the confounding influences from altered maternal glucose metabolism by metformin which is seen in diabetic conditions.

Methodology- Pregnant C57BL/6 mice received either metformin (5 mg/mL) in drinking water or plain water (control) from E0.5 until delivery. At 8 weeks of age, the offspring were placed on either a high-fat diet (HFD) or control diet until the end of study. At 28 weeks, oral glucose tolerance tests (OGTT) and metabolic assessments using indirect calorimetry were conducted. Pancreatic tissues were collected for immunohistochemistry.

Results- Maternal treatment did not affect offspring birth weight. Offspring on the HFD gained significantly more weight than those on the control diet, regardless of maternal metformin treatment. In female offspring, HFD led to increased gonadal and inguinal white adipose tissue and brown adipose tissue weights, irrespective of maternal treatment while this was not observed in males. HFD-fed offspring also showed impaired glucose tolerance, with elevated insulin and blood glucose levels during OGTT. However, maternal metformin treatment did not influence offspring body weight, fat accumulation, glucose or energy metabolism parameters.

Conclusion- These findings suggest that offspring exposed to metformin in utero did not show increased risk of obesity or metabolic dysfunction, even when challenged with a high-fat diet. This further suggests that gestational metformin is unlikely to cause direct harm to long-term metabolic health and development in offspring.