Gestational diabetes mellitus (GDM), defined as glucose tolerance disturbances during pregnancy, is this period's most common metabolic complication. Maternal hyperglycemia affects the fetal hormonal response and insulin synthesis, which is crucial for its development and may program its metabolism. GDM increases the risk of obesity, metabolic syndrome, type 2 diabetes (DM2), and cardiovascular disease in the offspring later in life. Prompt diagnosis of hyperglycemia in pregnancy and effective and safe (for mother and fetus) therapies regulating maternal glucose levels are essential for the proper development and maturation of fetal tissues and organs.

Metformin is an oral biguanide that works primarily by inhibiting hepatic gluconeogenesis, and it also increases glucose uptake in peripheral tissues and reduces glucose absorption in the gastrointestinal tract. Metformin does not directly affect insulin secretion and therefore does not cause hypoglycaemia, which makes it safer than other drugs for diabetes.

Metformin is now called the gold standard in the treatment of type 2 diabetes and insulin resistance in many countries and is one of the most prescribed drugs in the world. It is also used for women suffering from polycystic ovary syndrome. The potential anti-cancer and anti-aging activity is also gaining more and more attention.

However, the treatment of GDM with metformin is debatable. For many years, the Polish Diabetes Society has maintained the lack of recommendation for using metformin in pregnant women. Unlike insulin, metformin crosses the placenta and is present at clinically relevant concentrations in fetal and placental tissues, which means that it has potential effects on a developing fetus. There are also no studies on the long-term effects of metformin exposure in utero. The available data come from studies of children, which does not allow determining the entire risk of diseases, including metabolic disorders that appear in the fourth or fifth decade of life.

The project aims to investigate the effects of maternal treatment with metformin in pregnancy and lactation on the trajectory of offspring development and possible changes in their epigenome. The experiments will be carried out on an animal model. Female rats with experimentally induced GDM will be treated with metformin or the combined therapy: metformin and insulin during pregnancy and lactation. The offspring will be tested at the following time points: 1st day of life, the 21st day of life (the moment of weaning), 20th week, and 18th months (about 40-45 years of life in terms of human lifespan).

In tissues involved in maintaining blood glucose homeostasis (liver, adipose tissue, intestine, muscle), tissue-specific parameters of development and maturation, markers related to cell metabolism, pro-inflammatory factors, and the pathway of metformin activity in the cells will be investigated. In addition, the effect of maternal metformin treatment on the epigenetic mechanisms, which shapes the epigenome of the offspring will be also investigated. Changes in the epigenome, i.e., epigenetic modifications, can significantly impact the offspring's health.

The author of the project hopes that the obtained results will contribute to understanding the hitherto unknown impact of metformin treatment in pregnant women on the health of the offspring in adulthood and will be used to develop an effective and safe treatment for gestational diabetes.