One of the global problems in the public health sector is malnutrition, the consequences of which include overweight and obesity. Excess body weight already affects one-third of all women of childbearing age. For these women, pregnancy is associated with an increased risk of abnormal course and health complications for both mother and child. Research on the impact of the mother's high-calorie (rich in fat) food on the health of the offspring is of wide interest to the scientific community. Although most of the work has focused on metabolic diseases, confirming an increased predisposition to obesity and type II diabetes in offspring, there is a need to expand research and understand the implications of this phenomenon for normal brain development in offspring. This is especially true in the context of searching for the reasons for the rapid increase in the number of patients diagnosed with neurodevelopmental diseases, including autism spectrum disorder (ASD) in recent decades. Core symptoms of ASD, such as difficulties in communication, and emotional control in people with ASD often make it impossible to lead a normal life in society and significantly reduce the quality of life. It is now widely recognized that the development of ASD is caused by a complex interaction between genetic and environmental factors, but the exact pathogenetic mechanisms are still not sufficiently understood. Moreover, recent considerations on the pathogenesis of ASD put the main emphasis on the period of intrauterine development (1-3 trimester of pregnancy) and the initial postpartum periods, characterizing ASD as a multistage, progressive disorder of brain development.

Recent literature, including the work of our team, highlights the impact of maternal obesity and exposure to a high-fat diet during pregnancy and lactation at an increased risk of ASD symptoms in the offspring. However, little is known about the processes by which an inappropriate intrauterine development and early childhood environment disrupt the normal pattern of brain maturation in offspring. To fill this gap, the main aim of the project is to thoroughly investigate and understand the role of exposure on high-fat diet and altered gut microbiota and its ability to produce and modify metabolic, immune, and neurochemical factors that ultimately affect the normal development and function of the offspring brain. In the next stages, we plan to investigate how maternal obesity, through disturbances in the intestinal microbiota, contributes to the molecular changes in the brain of adolescent offspring, important for the pathogenesis of ASD, including the mTOR signaling pathway (controlling e.g., processes related to the proper functioning of neurons) and the balance between excitatory and inhibitory neurotransmission. In addition, we will use magnetic resonance (MRI) neuroimaging techniques to search for structural and functional biomarkers of ASD development in offspring at risk of maternal obesity, which could be used in the subsequent non-invasive diagnosis of this disorder in children.

ASD is most often diagnosed in early childhood, usually in young children. Thus, it must be assumed that the atypical brain function begins long before the neurons are fully mature. The question then arises whether, if atypical brain development becomes apparent already in the prenatal stage, will it not be too late to treat children after the first diagnosis of symptoms to reverse the unfavorable changes? Therefore, we will also assess the effect of probiotic supplementation (*Lactobacillus rhamnosus* and *Lactobacillus helveticus*) or pharmacological intervention using the antidiabetic drug – metformin during pregnancy and lactation in the prevention of the development of an autistic-like phenotype and abnormal brain development in offspring exposed to maternal obesity induced by a high-fat diet. The search for new indications for old drugs with a confirmed safety profile is an increasingly desirable strategy that saves time and resources that would have to be consumed in research into completely new drugs. The potential efficacy of probiotic or pharmacological interventions during pregnancy and lactation in reducing the development of the core symptoms of ASD will be confirmed in BTBR mice, a preclinical mouse model of idiopathic ASD.

Project results will significantly increase our understanding of the role of maternal gut microbiota altered by a high-fat diet in the abnormal development of the offspring's brain, which may be manifested by symptoms characteristic of ASD. In addition, thanks to the use of modern and non-invasive tests using MRI and the assessment of the effectiveness of probiotic and metformin, the project may contribute to the identification of diagnostic biomarkers and safe forms of ASD prevention, which are currently not available.