The aim of the project is to determine the importance of WWOX gene in the pathogenesis of gestational diabetes by its involved in the control of glucose metabolism. The aim of study is to investigate molecular mechanisms, by which, WWOX protein determines the cell metabolism and what kind of disturbances take place in these processes in gestational diabetes mellitus and role of WWOX expression level in cellular response on hyperglycemia and hypoxia. Currently, WWOX gene is best known as a suppressor, which expression loss or reduction is observed in many types of cancer. However, in addition to neoplastic changes in mice lacking WWOX expression, authors demonstrated metabolic abnormalities, including hypoglycemia. Moreover, experiments on the mouse fibroblasts MEF was aso conducted and determined that absence of WWOX expression inhibits the aerobic metabolism and moving the glucose metabolism in the direction of glycolysis. Furthermore, it was shown that the WWOX implicated as a negative regulator of the hypoxia inducible factor HIF1A. In this way, WWOX also is indirectly responsible for controlling the expression of genes involved in glycolysis, which expression is dependent on the hypoxia inducible transcription factor HIF1A. There are described more than 200 WWOX partners among which there are present proteins involved in the metabolism of glucose, gestational diabetes genetic risk factors and risk factors associated with type 2 diabetes. All these reports allow us to hypothesize about the importance of WWOX in the control of glucose metabolism. One of metabolic diseases characterized by disorders of carbohydrate tolerance is gestational diabetes mellitus. In normal pregnancy, insulin resistance is a physiological process resulting from the need to provide glucose to the fetus. For healthy pregnant women, the increase of insulin resistance is compensated by increased secretion of insulin by the pancreas β cells, whereas effectiveness of this process is reduced in case of women with gestational diabetes. After completion of pregnancy diabetes symptoms disappear, but having gestational diabetes mellitus increased more than a 7-fold risk of developing type 2 diabetes in period 5 to 10 years after delivery. Another problem associated with hyperglycemia is hypoxia in the placenta as a result of too high glucose concentration. In the first trimester of pregnancy, conditions of reduced oxygen content are necessary for the proper development of the placenta, but later oxygenation returns to normal levels. In contrast, elevated blood sugar level causes chronic hypoxia stress, which may be a reason of impaired fetal development. The main transcription factors activated in case of hypoxia conditions are HIF family. Under normal oxygenation HIF1A subunit is hydroxylated and degraded in proteosomie. Hypoxic conditions inhibit this process by allowing the creation of active complex transcription factor activity. As already mentioned earlier, WWOX is one of the known factors, which by interaction with HIF1A modulates HIF1A levels and inhibits its function. In his way, WWOX prevents expression of gene dependent on HIF1A.

Our preliminary studies of peripheral blood leukocytes of patients with GDM in relation to the control group of healthy pregnant women showed increased of WWOX and HIF1A expression level. Despite this, the ratio of WWOX / HIF1A expression in patients with gestational diabetes is almost two fold lower in relation to the control group. This allows us to suggest that the expression level WWOX in the case of gestational diabetes is too low to effectively act as a negative regulator of HIF1A factor.

Objective 1. The aim is to determine the differences in the expression level WWOX in peripheral blood leukocytes for patients with gestational diabetes relative to the control group of healthy pregnant women.

Objective 2. Determination of the expression profile of genes involved in glycolysis and the development of diabetes and changes in the metabolism of glucose, depending on the level of expression in the cell model WWOX.

In the first stage of the project we are planning further examination of the expression level of WWOX, HIF1A and genes involved in glucose metabolism in patients diagnosed with gestational diabetes mellitus in relation to the control group of healthy pregnant women. The next stage of the project is to create a cellular model of conditions in the placenta of women with gestational diabetes. For this purpose, the human fibroblast cell line is subjected to culture in the presence of hyperglycemia and hypoxia. In addition, to determine the role WWOX cellular response to the above conditions, the cells will be transduced with a viral vector to overexpress or silence the level of its expression. Obtaining these variants of cell lines, we will examine differences in glucose metabolism between them and changes in the expression level of genes involved in glucose metabolism and which are risk factors of diabetes. More of examined genes are predictive WWOX partners.