Homocysteine (Hcy) is an amino acid produced in the metabolism of methionine. It is an essential type of amino acid gained from the daily diet. Elevated levels of Hcy called Hyperhomocysteinemia (HHcy) is caused by numerous factors, such as genetic defects, lack of folic acid, vitamin B6 and B12 deficiency, hypothyroidism, drugs, aging, renal dysfunction and high methionine diet. The estimated prevalence of mild HHcy is 5 to 7% in the general population. Hcy is an independent risk factor of cardiovascular and neurodegenerative diseases. Recent studies have reported that HHcy was associated with numerous pregnancy complications in humans. Besides, we discovered that HHcy induced during pregnancy led to increase in-utero death and reduced neonatal birth weight. Identifying risk factors for unsuccessful reproduction, and understanding how HHcy may influence embryo development is of particular importance for public health policy in our society.

The goal of this project is to understand/reveal molecular mechanisms by which HHcy influence development of early embryos and causes pregnancy complications.
Our main hypothesis is that HHcy disturbs epigenetic marks -the triggers or silencers of transcription machinery in oocytes and early embryos which lead to impaired expression of essential genes for embryo growth and development. To test this hypothesis, we propose the following specific aims:

Aim 1: Elucidate mechanisms by which dietary HHcy impairs oocytes potential for maturation and fertilization by 1a) comparing HHcy influence oocyte development in vitro after its activation, 1b) checking if HHcy changes mitochondrial content, activity, and mtDNA copy number in oocytes.
Aim 2: Analyse HHcy-induced epigenetic changes in pre-implantation embryos: 2a) we will determine how HHcy affects activity of enzymes that methylate DNA and we will check global DNA methylation levels; 2b) Examine how HHcy changes gene expression and chromatin accessibility in embryos and; 2c) Analyse HHcy-induced changes in the morphology and differentiation of pre-implantation embryo
Aim 3: Examine the effect of dietary HHcy on placenta development by analysis morphology, implantation sites, and other important features of a properly formed placenta.

Significance: This study will elucidate unknown mechanisms of Hcy-induced changes in embryo/placenta development and provide new insights into the origins of pregnancy pathologies caused by dysregulation of Hcy metabolism. The knowledge gained during this study may be used for prevention and/or treatment of reproduction pathologies associated with HHcy, also considering improvement of the Assisted Reproductive Technologies (ART) in human medicine.