Summary

The endometrium is a uterine tissue that plays a pivotal role during the course of early pregnancy and provides an appropriate intrauterine environment, among others, necessary for proper implantation and development of the embryo. Molecular mechanisms involved in the regulation of reproductive processes in females and the proper functioning of the uterus are influenced by environmental factors such as temperature, stress, chemical pollutants, and diet. These factors also include extremely low-frequency electromagnetic field (ELF-EMF). The presence of ELF-EMF is related not only to its natural sources in nature (Earth, Sun), but also to technological development and industrialization, the consequence of which is currently an increase in the number of ELF-EMF emitters in the environment. The results of previous research conducted on the domestic pig model (*Sus scrofa domestica*, L.) during the peri-implantation period have shown that exposure of endometrium to ELF-EMF may have a significant impact on the course of numerous biological processes determining the reproductive success of females.

It was found that, as a consequence of *in vitro* exposure of the endometrium of pigs to ELF-EMF (50 Hz, 2 h, 8 mT) during the peri-implantation period, changes occurred in the mechanisms of epigenetic regulation of gene expression, apoptosis, and oxidative stress. It has been shown that exposure of endometrium to ELF-EMF causes an increase in the level of DNA methylation in the promoter region of genes with differential expression (DEGs) changed under the ELF-EMF exposition, which are involved in cell proliferation and differentiation (*i.e*. *EGR2*, *ID2*), luteal maintenance and stimulation of angiogenesis (*PTGER4*) and a decrease in the level of DNA methylation of the promoter regions of *IL1RAP* and *NOS3*, involved in the intracellular complex, cell signaling for the IL1β system and nitric oxide (II) production, respectively. No changes in DNA methylation levels were observed in the case of *HSD17B2*, *MRAP2*, *SERPINE1*, *VDR* and *ZFP57*. Changes in the level of DNA methylation in the endometrium caused by tissue exposure to ELF-EMF may cause changes in the transcriptomic profile of the endometrium and lead to disruption of physiological processes accompanying implantation and development of embryos.

The observed changes in DNA methylation levels in the endometrium exposed to ELF-EMF prompted to investigate whether tissue exposure to ELF-EMF contributes to

changes in the potential for DNA methylation, expressed by the mRNA transcript and protein abundance of DNA methyltransferases (DNMTs), *i.e*. DNMT1 and DNMT3a, responsible for maintaining methylation and *de novo* DNA methylation, respectively. In the endometrium exposed to ELF-EMF, a decrease in the DNMT1 mRNA transcript and protein abundance and an increase in the DNMT3a mRNA transcript and protein abundance were found. Changes in the UHRF1, MBD1 and EZH2 mRNA transcript and protein abundance have also been documented, which interact with DNA methylation or histone methylation and acetylation, thus contributing to the reduction and/or silencing of gene expression. An increase in the activity of histone deacetylases (HDACs), responsible for catalyzing the reaction of detaching acetyl groups (-$COCH_3$) from the N-terminal histone chains and increasing the degree of chromatin condensation, was also demonstrated. There was also a decrease in *DGCR8* mRNA transcript abundance and an increase in the DICER1 and DGCR8 mRNA transcript and protein abundance, responsible for microRNA biogenesis. In summary, ELF-EMF has the potential to induce changes in mRNA transcript and protein abundance of important elements related to the epigenetic regulation of gene expression in the endometrium. The identified changes may be the cause of the observed changes in the transcriptomic profile of the endometrial tissue exposed to ELF-EMF, which in turn may disrupt biological processes occurring in the pig uterus during the peri-implantation period.

Based on the functional analysis of NGS results, which showed an increase in the *CIDEB*, *GADD45G* and *TP53I3* mRNA transcript abundance, involved in the induction of apoptosis and cellular response to stress (including oxidative stress), it was examined whether exposure to ELF-EMF may affect the process of apoptosis and/or oxidative stress in the endometrium of pigs during the peri-implantation period. There was a decrease in the CASP7 mRNA transcript and protein abundance and an increase in the NOS3 mRNA transcript and protein abundance, which are involved in the process of apoptosis and the synthesis of nitric oxide (II), respectively.

In conclusion, it has been documented that ELF-EMF can affect the potential to DNA methylation and DNA methylation level, histone acetylation, microRNA biogenesis, apoptosis and oxidative stress in the endometrium of pigs during the peri-implantation period. The observed changes may contribute to impaired cell proliferation, angiogenesis, secretory activity and receptivity of the examined tissue, which may affect the intrauterine environment and the implantation process.