Description for the general public

The female reproductive system contains two main parts: the uterus and ovaries. The major function of ovaries is the release of mature egg cells for fertilization and production of steroid hormones. Those hormones are important to prepare the lining of the uterus (endometrium) for pregnancy. Precise mechanisms involved in the regulation of the reproductive system development and differentiation are essential for the successful propagation of a species. Both fetal and neonatal periods of development are critical in establishing the ovarian follicle number that will provide the female with enough egg cells for a lifetime of fertility. In addition, the proper development of the uterine gland during the neonatal period is required for the functional capacity of the adult uterus to support pregnancy. It is well known that developmental events associated with 'neonatal programming' of ovarian and uterine functions are, *inter alia,* under the control of hormones. Therefore, there is a growing concern regarding the adverse impact of endocrine active chemicals (EACs) on animal and human reproduction. EACs, arising from many different sources (e.g., pesticides, industrial chemicals, pharmaceuticals and phytochemicals), may interfere with the regulation of endocrine systems by mimicking or blocking functions of natural hormones. Our previous studies involving neonatal piglets demonstrated that changes in the androgen and estrogen milieu using EACs with androgenic/antiandrogenic and estrogenic/antiestrogenic activities affected ovarian development and function and caused long-term effects observed in adult life. On the other hand, bioactive components of the mother's milk are additional factors influencing human and animal development during the neonatal period. The long-term positive health effects of breast milk are scientifically accepted and World Health Organization highly recommends breastfeeding in the first six months of life. Consequently, it is important to study the protective effects of natural breast milk feeding during EACs exposure. Therefore, the main goal of the current project is to recognize the potential protective effects of mother's milk against EACs action in ovaries and uterus of neonatal pigs. In addition, by using *ex vivo* experimental models – ovarian and uterine tissue explants incubated with selected EACs – we will be also able to examine the solely impact of EACs, excluding other external factors, which may affect ovarian and uterine tissue development. The pig as a model organism has a high relevance for biomedical research since its anatomy, genetics and physiology reflect human biology more closely than classic rodent models. To meet our goals, ovarian and uterine explants, obtained from 10-day-old sow-fed or formula-fed piglets, were incubated with selected EACs: antiandrogen, estrogenic alkylphenol and organochlorine pesticide possessing estrogenic, antiestrogenic and antiandrogenic properties, and the transcriptomic approach combined with various functional studies will be employed in the current project. A transcriptomic approach and microRNA-mediated regulation of gene expression are hot topics for research over the past decade. Indeed, results of our previous studies suggested that the long-term effect of neonatal exposure to EACs on the porcine luteal tissue is mediated by altered expression of microRNAs. Moreover, it was reported that EACs increase oxidative stress (*via* reactive oxygen species [ROS] production and altering the activity of antioxidative enzymes), and imbalance between pro-oxidants and anti-oxidants can lead to a number of reproductive disorders such as endometriosis, polycystic ovary syndrome (PCOS), and infertility. Therefore, sets of experiments are planned to study - in ovarian and uterine explants of piglets fed with mother's milk and milk replacer - the effect of neonatal exposure to examined EACs on (1) mRNA transcripts and the microRNA profile, (2) ROS production and antioxidant enzymes activity, (3) proliferation and apoptosis, (4) abundance of proteins involved in formation of ovarian follicles and uterine glands as well as (5) expression of enzymes involved in microRNA biogenesis.

Many female reproductive disorders originate from misregulated physiological processes which take place during the neonatal period – a critical stage for the establishment of reproductive potency. Everyday use of many endocrine active chemicals is already prohibited, as their harmful impacts on reproduction and health have become known. Nevertheless, market introduction of new chemicals with potential deleterious influence on reproductive physiology has continued. Although EACs are known to negatively affect female reproduction, the protective effect of mother's milk has not been extensively studied. Therefore, elucidating the molecular mechanisms responsible for adverse effects of EACs action on neonates and in addition, information as to whether ovarian and uterine tissue responses to EACs differ between animals fed mother's milk and milk replacer may inspire further research on the female reproductive potential and consequently, will help to gain better control over this potential.