

Epidemiological studies showed a link between problems with offspring of couple living in contaminated environment in comparison those who live in an uncontaminated environment. In addition, interest in this problem is due to the increasing number of difficult to explain the reasons for infertility, and moreover available data showed hormonal activity of the compounds present in the environment, their presence in serum, follicular fluid and adipose tissue. Dysfunction of endogenous hormones is one of the possible mechanisms of xenobiotic action. Another possibility is induction of apoptosis and in consequence causes disruption of ovarian follicular development, atresia, and inhibition of steroidogenesis and death of oocyte. Unidentified reason of infertility may be due to increased accumulation of xenobiotic in serum and follicular fluid, disruption of detoxification, differences in the expression of steroid and aryl hydrocarbon receptor (AhR) as well as differences in cell response to stimulation with gonadotropins.

In the available literature, there are reports indicating significant higher levels of polycyclic aromatic hydrocarbons (PAH) in cord blood and maternal blood. PAHs are industrial compounds or combustion byproducts that widely contaminate the environment. Exposure of PAHs can come from both occupational and environmental sources arising from use of coal tar, fires at oil wells, exposure to automotive exhaust gases, tobacco smoke and crude and mineral oils as well as incomplete combustion of fossil fuel and many other sources. Due to their persistence in the environment and their potential toxicity, 16 homocyclic PAHs: naphthalene, acenatarn, fluorine ,anthracen, fluoranten, piren, benzo/a/antracen, chrysene, benzo/a/antracen, chryzen, benzo/a/fluoranten, benzo/k/fluoranten, , benzo/a/piren, indeno/1,2,3-cd/piren., dibenzo/a,h /antracen, benzo/g,h,i/perlyen, have been identified as priority pollutants by both the US Environmental Protection Agency and the European Commission. Conducted research concern predominantly carcinogenic potential of benzo (a) pyrene, however, in addition to the proven, for benzo (a) pyrene, carcinogenic properties it have been showed that PAHs exhibit estrogenic, androgenic and anti-estrogenic activity. Our preliminary studies indicated differences in the 16 marker PAH accumulation in mother blood and cord blood. Moreover this preliminary data showed higher percentage distribution of fluoranthene, pyrene and benzo (a) anthracene in cord blood than in maternal blood confirming perinatal exposures for PAH, so apart from exposure during adulthood, perinatal exposures should be also consider.

The most information on the impact of environmental contaminants on human health comes from studies in animals exposed to individual chemicals. People are exposed not for a single compounds, but mixture present in food, water or air. Our previously published data showed differences in action a single toxic compounds (mostly respondents) and mixtures of compounds occurring in the environment on ovarian follicular function: e.g. mixture of low and high chlorinated biphenyls (PCBs), mixture of PCBs and pesticides, mixtures of polybrominated dibenzo ethers (PBDEs) and pesticides as well as mixtures of polychlorinated naphthalene.

The aim of the project will be to determine the direct impact of PAHs mixtures on aromatic hydrocarbons receptor (AhR), which is the mediator of the toxic effects of PAHs, but also play an important role in physiological processes, and to demonstrate whether exposure to mixtures of PAHs might be responsible for the induction of follicular atresia and disruption of steroidogenesis.

PAHs, after binding with AhR receptor and formation complex of AhR-PAHs does not binding with the nuclear AhR activator (ARNT) but the nuclear AhR repressor (AhRR) and in the consequence leads to the inhibition transcription of genes responsible for detoxification, apoptosis and ovarian cell steroidogenesis.

We plan the use of human cell lines granulosa hGrC1. Human granulosa cell line hGrC1, non-luteinizing granulosa cells which is a good model to investigate action of different factors on folliculogenesis. 4 different mixture based on concentration in mother blood and cord blood well be used. The mixture of 1 and 2 will comprise all 16 compounds in amounts present in the mother and fetus blood. The mixture of 3 and 4 will include naphthalene, phenanthrene, fluranten, anthracene, pyrene and benzo (a) pyrene present in a larger amount in of fetal than in maternal blood.

In the first stage we plan to investigate effect of mixtures on gene and protein expression of aryl hydrocarbon receptor (AhR), aryl hydrocarbon nuclear translocator (ARNT), and aryl hydrocarbon nuclear repressor (AhRR). Next, using the ARNT or AhRR gene silencing determine the influence of mixtures on the activation of enzymes I and phase II of metabolism (CYP1A1, and COMT), expression caspase-3, as executive enzyme of apoptosis and on basal and FSH stimulated estradiol secretion.

This will be the first such widely conducted studies on the consequences of exposure to mixture of PAHs accumulated in the high amount in maternal and cord blood on the endocrine functions of the ovarian follicles and indicated new molecular mechanism of action.