The ovary is a source of steroid hormones and female germ cells called oocytes that are enclosed in the ovarian follicles, the fundamental units of the ovary. All follicles start as a primordial follicle, among them some will eventually develop to the preovulatory stage. Unlike testes, ovaries do not produce gametes throughout whole life: in all mammals the setting up of the oocytes' reserve occurs during fetal or neonatal life. This reserve established by primordial follicle pool is incredibly important for fertility and represents the total population of oocytes during female reproductive lifetime. Control of follicular reserve and entry of follicles into the growth path towards ovulation or atresia (degeneration of follicle) are not well understood. In recent years, research has demonstrated that control of primordial follicle activation requires complex bidirectional signaling between the oocyte and the surrounding somatic cells. During follicular growth, cell proliferation and cell death are present simultaneously. Many female reproductive disorders originate from the neonatal period which is a critical stage towards the reproductive potency. Over the past decades there have been an increasing number of attempts to better understand the role of steroid hormones signaling, especially androgen and estrogen, signaling within the ovary during fetal and neonatal developmental periods. Looking at different aspects of follicular development following androgen stimulation in various species, in vivo and in vitro studies demonstrated direct androgen effects on folliculogenesis. It has been revealed that androgens stimulate the initiation of follicular recruitment, stimulation of early stages of follicular growth, and increase in the number of growing follicles. Moreover, estradiol was shown to play a critical role in somatic cell differentiation into pregranulosa cells leading to the primordial follicles formation and development. However, whereas estradiol at relatively lower levels supports somatic cell and oocyte interaction during the critical phase of cell assembly, at higher levels it adversely suppresses the process of primordial follicle formation.
Endocrine-active chemicals (EACs) which arise from many different sources (pesticides, industrial chemicals, pharmaceuticals and phytochemicals) may interfere with the natural regulation of endocrine systems by either mimicking or blocking the function of natural hormones. Exposure to these compounds during critical periods of development can affect gonad formation and disrupt reproductive functions during adulthood. It is therefore important to study the effects of chemicals that antagonize or mimic the function of androgens and estrogens to establish their role in ovarian follicle assembly, activation and development. The irreversible premature oocyte activation may lead to rapid depletion of follicle reserve, leading to a demise of ovarian function similar to premature ovarian failure (POF).
The pig has recently become increasingly relevant as a model organism for biomedical research due to the fact that its anatomy, genetics and physiology reflect human biology more closely than the classic animal models. In many mammals, including pigs, folliculogenesis (process of ovarian follicle formation and development) begins during fetal development and continues throughout adulthood. The assembly of primordial follicles and their subsequent transition to the primary stage occur in the late gestational and neonatal period. Therefore, it seems possible that neonatal exposure to compounds that mimic or antagonize androgen and estrogen action may disturb the normal process of folliculogenesis. Previously, we have demonstrated that neonatal exposure of piglets to the antiandrogen flutamide affects ovarian follicle development, as well as the corpus luteum formation and function during adulthood. Thus, starting from the literature and our previous research, the objective of the present research is to clarify if neonatal exposure to endocrine-active chemicals (between days 1 and 10 of neonatal life) influences the early stages of follicle development in pigs. The specific objectives of this project are to determine whether compounds mimicking or blocking the function of androgens and estrogens may alter the proportion of primordial and growing follicles, proliferation, apoptosis and autophagy rate in the 11-day-old porcine ovaries.
Both autophagy and apoptosis play an important role in determining cellular fate. They participate in development, cellular homeostasis, and both physiological as well as pathological processes. It is generally known that apoptosis and follicular atresia are important events during oogenesis and folliculogenesis. Apoptosis is the type I form of programmed cell death that is thought to be the primary mechanism by which the oocyte nests break apart and primordial follicles are formed. Ovarian follicular atresia is known to be regulated by androgens both directly and indirectly by their conversion to estrogens. However, recent evidence shows that other process, known as autophagy, is an alternative route in cellular elimination in the mammalian ovary. Autophagy is not only a process of cell death, it is also a cell survival mechanisms. Although autophagy functions initially as a cytoprotective mechanism, if cellular damage is too extensive, or if apoptosis is compromised, an increase in autophagy may kill the cell. Another puzzle is crosstalking between autophagic and apoptotic pathways which has been recently shown. Therefore, this project focuses on molecular mechanisms involved in apoptosis and autophagy in neonatal porcine ovaries exposed to selected compounds which is important to increase the knowledge on the effect of EACs with androgen/antiandrogen and estrogen/antiestrogen action on early follicle development in pigs. In the light of growing body of evidence that demonstrates the presence of EACs in the environment, understanding the mechanism of selected EACs action within neonatal porcine ovaries will provide a basic data for further research of the female reproductive potency.