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7. Endocrine disruptors and endometriosis: The role of BPA

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Abstract. Endometriosis is a chronic gynaecological disease characterized by the growth of endometrial tissue outside the uterine cavity. Exposure to endocrine disruptors during critical period of development causes long-lasting effects, being the genital system one of the targets. This article describes and discuss experimental evidences about the effects on female genital system caused by developmental exposure to the endocrine-disrupting chemical bisphenol a (BPA) during pre- and peri-natal development, with particular emphasis on endometriosis. The data presented suggest that endometriosis could be considered as a developmental disorder. This observation may induce to thoroughly reconsider the pathogenesis and treatment of endometriosis, considering the high incidence of this disease and the problems caused by associated infertility.

Endocrine disruptors exposure and reproductive functions

It is a very well documented fact that female reproduction efficiency has deteriorated over the last decades (1,2). Noteworthy, cultural changes in

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western countries (such as increased contraception or delayed childbearing) have potentially contributed to this phenomenon; however, it must be acknowledged the role of environmental factors exposures (3). Interestingly, a cause of reduced reproductive capacity of males linked to exposure to environmental factors has been deeply investigated and has raised also public interest (4). On the contrary, a comparable attention has not been dedicated to females. Nevertheless, the ability of synthetic chemicals to affect reproductive function and health in females has been demonstrated for the first time several decades ago, when the effects of diethylstilbestrol (DES) on the daughters of women given treatment with DES were firstly reported (5).

DES belongs to a family of chemicals that are able to mimic hormones and that are named endocrine disruptors. The most accepted definition for endocrine disruptors is “exogenous chemical substances or mixtures that alter the structure or function(s) of the endocrine system and cause adverse effects at the level of the organism, its progeny, populations, or subpopulations of organisms, based on scientific principles, data, weight-of-evidence, and the precautionary principle” (6). To date, a plethora of research studies have been conducted, clearly demonstrating the capability of endocrine disruptors to affect, even at very low doses the endocrine system and the correct development of mammalian and non-mammalian species (7,8). Interestingly enough, a wide series of experimental studies have proved also that the simple exposure to these chemicals during critical periods of development is able to cause several gynaecologic pathologies later in life, including predisposition to tumors, such as uterine adenocarcinomas, breast cancers or obesity, coronary diseases and hypertension (9-20). The most well accepted pathogenetic mechanism for this phenomenon indicates alteration in estrogen signalling, because of the crucial role of such hormone for proper ontogeny and function of the reproductive system (21).

In detail, the exact mechanisms through which endocrine disruptors induce these phenomenon are essentially still unknown; nevertheless, is widely accepted that the embryos are sensitive to environmentally induced reproductive abnormalities during a critical foetal exposure window (22). Actually, there are three possible different mechanisms to explain the influence of environmental factors on the developing foetus. First of all, an effect on gene expression induction, with particular interest on alteration in Hox gene expression in the developing mullerian system (23-25). It is well known the crucial role of Hox genes in the correct axial development of upper vagina, cervix and fallopian tubes from the primitive Mullerian duct (26). The second proposed mechanism, include epigenetic modifications of

DNA sequences, that are able to perturb transcriptional characteristics of some genes (27). The last mechanism hypothesizes a role for the nervous system that could be able to register the environmental perturbations and to produce an altered signalling to the endocrine system (28).

Bisphenol A (BPA) is historically considered the first reported synthetic chemical able to cause estrogen receptor modulation (29). It is, indeed, one of the more studied molecules among the chemicals belonging to the endocrine disruptor family, also because of the fact that it is one of the highest volume chemicals produced worldwide, (30) and it responsible for the great majority of the estrogenic activity that leaches from landfills into the surrounding ecosystem (31,32). Because of this enormous potential exposure of humans to BPA, in the last years several studies have attempted to analyse its bioremediation (33) and bio-determination (34) in polluted waters and several molecular mechanisms by which it interacts at cellular level, have been deeply studied (35-37). Coherently, different “low-dose” studies in mammals have linked perinatal BPA exposure to a multiplicity of irregularities in the female reproductive tract, including early onset of vaginal opening (38), early onset of puberty (39,40), altered estrus cyclicity (41), altered plasma levels of luteinizing hormone (42), and altered vaginal, ovarian and uterine histology (43-45).

Is endometriosis a developmental pathology?

Endometriosis is a very frequent gynecological disease characterized by the presence of endometrial glands and stroma outside the uterine cavity (46,47). The prevalence in the female population is 6-10%; nevertheless, in women with pain, infertility or both, the frequency surges to 35-60% (48). Peculiar symptoms of endometriosis are infertility, chronic pelvic pain and adhesion formation. Deep infiltrating endometriosis of recto-vaginal septum is a certain form of endometriosis located under the peritoneal surface (49). Indeed, pelvic pain symptoms are strongly associated with this peculiar form of endometriosis. This disease has a significant morbidity and high health care costs associated, thank to its prevalence in the female population; nevertheless, still today the definitive cause(s) of this disease are unsure and none of the pathogenetic theories proposed, such as retrograde menstruation implants, coelomic metaplasia or staminal cells hypotheses, has conclusively been proved (48). The influence of steroid hormones on endometriosis is widely accepted, since endometriosis glands and stroma display estrogen and androgen receptors and, even more important, estrogens can promote their growth and survival (50). Recently, our research group has demonstrated that

ectopic endometrium with a molecular and histological phenotype identical to that of the eutopic endometrium is detectable in a substantial number of human female fetuses analyzed by autopsy (51-54). In figure 1A a typical fetal endometriosis gland present in the recto-vaginal septum is depicted. We have proposed that specific molecular events during a critical window of time in the developing embryo could be responsible for perturbations of the fine-tuning mechanisms responsible for the correct progress and growth of the female genital system. This, in turn, would consent the displacement of endometrial tissue outside the uterine cavity during the earlier steps of organogenesis. Among the molecular events responsible of this phenomenon could be genetic and/or epigenetic factors of some organizational events associated with the development of the embryonic uterine wall. The increase in the incidence of endometriosis in patients affected by uterine malformations seems to support this hypothesis (54). Even more interesting, recent published data about utero-vaginal embryogenesis, strongly support the role of altered organogenesis in endometriosis pathogenesis (55). Finally, the description of endometriosis in non menstruating animals (56,57), also is in line with this hypothesis. Nevertheless, genomic wide analysis methodologies have allowed us to demonstrate that the transcriptional profiling of the ectopic endometrium is different from the corresponding eutopic one, especially because of the altered transcription of several genes involved in embryogenesis. Interestingly, this expression pattern was independent of the menstrual and hormonal phase (58). Among the genes differentially expressed, we found: a) LEFTY2, BMP2 and BMP4, three members of the transforming growth factor-beta super-family that include growth and differentiation proteins; b) GREM1 and FST (Follistatin), that are BMP antagonists; c) SERPINE1 and SERPINE2, members of the serine protease inhibitor (SERPIN) family that are involved in tissue remodelling.

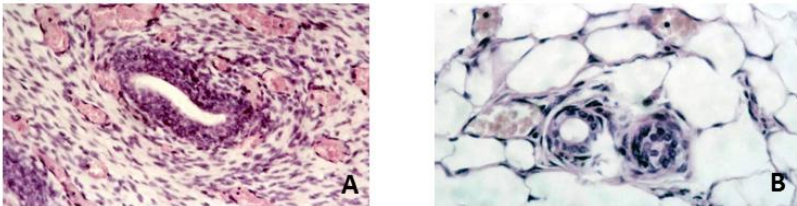


Figure 1 A: an endometriotic gland surrounded by stroma present in the recto-vaginal septum of a female fetus (Ematoxylin/Eosin, original magnification X10). **B:** a typical endometriotic structure visible in the peri-uterine area of a mouse exposed in utero to BPA (Ematoxylin/Eosin, original magnification X10).

All these observations have allowed us to deeply reconsider the pathogenesis of endometriosis and to potentially include it among the group of developmental pathologies (59).

Endocrine disruptors and endometriosis: The role of BPA

Accumulating experimental evidences clearly confirm the fact that BPA may act as a reproductive toxicant, although the real impact of human health is still debated (60). Most of the works on the effects of BPA on ovaries has been performed in animals, because in humans these organs and their function are largely inaccessible.

Concerning the ovary, it has been shown that maternal exposure to BPA affects the early stages of oogenesis in the developing fetal ovary, with resulting meiotic and prophase defects, that account for an increase in multiple oocyte follicles (61). Interestingly, our group has demonstrated a significant decrease in the number of primordial and developing follicles and an increase in the atretic follicles in the mice treated with BPA in utero respect to the control (62). This phenotype is in accordance with the very well described effects of endocrine disruptors on female reproductive disorders, such as altered cyclicity and fecundability, polycystic ovary syndrome, and precocious menopause (60).

BPA effects on the uterus include an increase in the thickness of the uterine epithelia and stroma in the offspring of pregnant rats exposed to BPA in the drinking water (63). Moreover, some tumorigenic effects can be elicited by BPA exposure during development; indeed, atypical hyperplasia, stromal polyps and sarcoma of the uterine cervix have been observed in adult female offspring exposed in utero to BPA (15). Finally, it has been also proposed that BPA exposure can lead to defective uterine receptivity (64).

Concerning a possible link between BPA exposure and insurgence of endometriosis, in a pilot study Cobellis et al (65) found a strict relationship between serum levels of BPA and the occurrence of endometriosis. In a similar work by Buck Luise et al (66), it has been found a positive association between urinary phthalate and endometriosis, while urinary BPA concentration was not associated with endometriosis. Finally Itoh et al. (67), failed to observe a direct link between urinary BPA concentration of a wide group of infertile patients and endometriosis. Therefore, the results are still controversial.

Leaving from this background, we decided to investigate the long-term effect of prenatal BPA exposure on the murine female reproductive tract with particular emphasis on endometriosis. We defined an experimental model, where pregnant mice were injected subcutaneously with 2% ethanol in

physiological saline solution (control) or BPA on day 1 of gestation through the seventh day after delivery. Female offspring were sacrificed at 3 months of age and pelvic organs analysed carefully. From this analysis, we found uterine abnormalities, consistently with previous works (68). More interestingly, we detected endometriosis-like structure in the adipose tissue surrounding the genital tracts of a consistent number of treated animals. An example of these endometriosis-like structures is depicted in figure 1B. The morphological and molecular characteristics of these endometriosis-like structures are exactly identical to that of the normal endometrium and stroma present in the uterus of the same animals. Indeed, not all the treated animals display an endometriosis-like phenotype. This phenomenon suggests that the exposition to endocrine disruptors during a critical window of prenatal development (69) might induce only in genetically predisposed animals the insurgence of endometriosis. The exact definition of this critical window for exposure during the prenatal development, as well as of the genetic background indispensable for the insurgence of the phenotype, will help in the comprehension of the pathogenesis and progression of endometriosis. To the best of our knowledge, this is the first animal model of endometriosis in mice.

In conclusion, we propose that endometriosis, should be considered among the complex of disorders caused by in utero exposition to endocrine disruptors. We would like to include all these disorders in a sort of syndrome of the female genital system, that would include endometriosis, progressive ovarian failure, infertility, precocious menopause, associated with specific symptoms such as headache, pelvic chronic pain, dysmenorrhea, dyspareunia, greater incidence of cancers, and many others, and it could be named syndrome of the ectopic endometrium. Considering the high incidence of endometriosis in humans and the enormous health problems caused by this disease, these observations should be analysed and possibly confirmed in greater experimental settings and the molecular basis carefully dissected.

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