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The influence of dioxines on endometriosis development – study review

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Abstract

Introduction: Dioxins and dioxin-like polychlorinated biphenyls are considered to be among the most toxic to humans due to their persistence, resistance to degradation and chemical properties. Endometriosis is characterized by the presence of endometrial cells outside the uterine cavity showing secretory activity. It is one of the most common causes of pelvic pain and decreased fertility; is formed as a result of the action of hormonal and immune mechanisms. The exact etiology is unknown and multifactorial; risk factors for endometriosis include both family conditions and various environmental factors, including exposure to chemicals.

The aim of the study: Evaluation of the impact of dioxins on endometriosis development.

Materials and methods: A research was performed using Pubmed, Google Scholar and ResearchGate; we made review and meta-analysis of the most relevant studies.

Results: Dioxins can contribute to cancer development, which is well documented, as well as several conditions, such as sexual dysfunctions, oxidative stress and inflammation. Dioxins have similar structure to steroid hormones, so their main target are male and female gonads, thyroid gland and other organs in which steroid hormones are produced.

Conclusions: Endometriosis is a multifactorial disease, whereas dioxins are strong poisons that have an adverse effect on live organisms. Many epidemiological studies suggest that dioxins may significantly contribute to the development of endometriosis.

Key words: endometriosis; dioxins; dioxin-like factors; aromatic hydrocarbon receptor; exposure

Introduction: Dioxins are mainly considered as polychlorinated dibenzo-dioxins (PCDDs) and polychlorinated dibenzo-furans (PCDFs). Dioxins come from incineration processes of industrial, municipal and medical waste, pesticides production, fires or improper oil disposal processes. People are exposed to these toxins in the environmental or occupational way or through an accidental pollution. Studies show that main sources of exposure for people are: inhaled air (8%), skin (2%) and consumption of contaminated water and food (which makes it to about 90%).

Part of dioxins are metabolised and then eliminated, but the rest stays stored in adipose tissue¹. Of course, people vary in capacity to eliminate these chemicals, but the elimination rate also depends on the dose absorbed. However, dioxins and dioxin-like polychlorinated biphenyls are considered to be among the most toxic to humans due to their persistence, resistance to degradation and chemical properties.

The effect of dioxins on the human body is based on the interaction through the aromatic hydrocarbon receptor (AhR), of which they are exogenous ligands. The receptor regulates the expression of genes associated with the metabolism of xenobiotics, determines the proteasome-dependent degradation of steroid hormone receptors and modulates the activity of the immune system.

Endometriosis is characterized by the presence of endometrial cells outside the uterine cavity showing secretory activity. It is one of the most common causes of pelvic pain and decreased fertility; about 10–15% of women at reproductive age suffer from pelvic pain and endometriosis². Usually, diagnosis is delayed for many years, the incorrect diagnosis is common, and there is no effective therapy³. Symptoms of endometriosis either include reduced fertility, chronic pelvic pain syndrome⁴, dysmenorrhea, dyspareunia or the disease is completely asymptomatic.

Diagnostics of the disease start from a basic interview, physical examination, gynecological examination to transabdominal, transvaginal, transrectal ultrasound – TRUS, magnetic resonance imaging and laparoscopy (which is a gold standard in the assessment of pelvic organs, assessing the patency of the fallopian tubes and the location of endometriosis foci, fibroids and adhesions).

Endometriosis is formed as a result of the action of hormonal and immune mechanisms.

There are a few pathomechanisms that can be responsible for this condition – regurgitation⁵, implantation or metaplasia, induction. The exact etiology is unknown and multifactorial; risk factors for endometriosis include both family conditions and various environmental factors, including exposure to chemicals.

Purpose: To evaluate the impact of dioxines on endometriosis development.

Material and methods: We did a research using Pubmed and Springer; then we made review and meta-analysis of some interesting studies. We searched for studies describing what dioxines are and analyzing the relationship between exposure to them and adverse health effects, especially the incidence of endometriosis.

Description of the state of knowledge:

Dioxins are known to bind to the AhR receptor (aryl hydrocarbon receptor) which is a receptor belonging to the family of transcription factors - basic helix-loop-helix (bHLH)⁶.

The aryl hydrocarbon receptor not only is present in the reproductive tracts of both males and females⁷, but also in the whole immune system – thus, it can modulate both inflammatory and immune reactions. It is a crucial compound in maintaining organism's homeostasis and combating infections⁸.

AhR stays within the cytoplasm when it is inactive; once the receptor is activated when a ligand binds, AhR reveals NLS (nuclear localization signal); then it transfers to the nucleus, forming a heterodimer with ARNT (aryl hydrocarbon receptor nuclear transporter)⁹. The ligand binding AhR seems to be important as it determines the rate of AhR activation¹⁰, influencing on the transcriptional activities.

Also, AhR plays an important role in detoxification as the AhR/ARNT dimers induce P450 genes transcription¹¹.

All in all, AhR modulates many cellular processes, thus the activation of this receptor by an inappropriate ligand can cause many incorrect alterations to human's organism and boost diseases¹².

Main known effects of dioxins include disturbances of normal hormone secretion, skin allergies and rashes (the best known is chloracne), they can promote oxidative stress and inflammatory processes, they cause systemic disorders, as growth disorders, they promote

susceptibility to infections, defects in the enamel, sexual dysfunctions, diabetes and insulin resistance, hyperpigmentation of the skin and cancer (mostly gastrointestinal and lymphatic)¹³.

A good example of a study showing the relation between dioxins and endometriosis is a research analyzing endometriosis development in monkeys in relations to 4-year dioxin exposure. The experiment was conducted on 24 monkeys. They were divided into 3 groups after 8 individuals. The control group was not exposed to TCDD exposure, the second group received a dose of 5ppt, and the third 25ppt. During the first years in the control group, the death of 2 animals (due to their age) was noted, in the second group there was a death of 1 individual (which was unclear) and the death of 4 animals in group 3 (3 of them of due to extensive endometriosis).

After 10 years, surgical laparoscopy was performed. The results showed that there is a direct correlation between disease and exposure to dioxin. The disease severity depended on the dose of dioxin. In the control group 2 out of 6 individuals suffered from minimal endometriosis, in the second group 5 out of 7 monkeys showed its symptoms, while in the third group only 1 individual was free of the disease¹⁴.

Summary:

To conclude, on the basis of many relevant studies, it is clearly visible that dioxins contribute to many conditions and alterations in human's system. They are related with diseases such as cancer, skin problems and inappropriate hormone secretion¹⁵.

The dioxin complex:AhR in clinical trials has shown a suppressive effect on the transcription of genes encoding estrogen receptors; in this way, dioxins significantly contribute to the development of endometriosis and hormonal disorders and have a general harmful effect on the human body.

Dioxins demonstrate similar structure to steroid hormones, so their main target are male and female gonads, thyroid gland and other organs in which steroid hormones are produced.

The experiment on rhesus monkeys and dioxins can be a good start point for further researches on the endometriosis and environment pollution.

References:

- ¹Marinković, Natalija, Pašalić, Daria, Ferenčak, Goran, Gršković, Branka and Rukavina, Ana. "Dioxins and Human Toxicity" *Archives of Industrial Hygiene and Toxicology*, vol.61, no.4, 2010, pp.445-453. <https://doi.org/10.2478/10004-1254-61-2010-2024>
- ² Mehedintu C, Plotogea MN, Ionescu S, Antonovici M. Endometriosis still a challenge. *J Med Life*. 2014 Sep 15;7(3):349-57. Epub 2014 Sep 25. PMID: 25408753; PMCID: PMC4233437.
- ³ Taylor HS, Kotlyar AM, Flores VA. Endometriosis is a chronic systemic disease: clinical challenges and novel innovations. *Lancet*. 2021 Feb 27;397(10276):839-852. doi: 10.1016/S0140-6736(21)00389-5. PMID: 33640070.
- ⁴ Sachedina A, Todd N. Dysmenorrhea, Endometriosis and Chronic Pelvic Pain in Adolescents. *J Clin Res Pediatr Endocrinol*. 2020 Feb 6;12(Suppl 1):7-17. doi: 10.4274/jcrpe.galenos.2019.2019.S0217. PMID: 32041388; PMCID: PMC7053437.
- ⁵ Ukrainets RV, Korneva YS. [Endometriosis of the ureter from the standpoint of implantation theory: some aspects of pathogenesis and clinical picture]. *Urologia*. 2021 Mar;(1):126-130. Russian. PMID: 33818948.
- ⁶ Bois FY, Eskenazi B. Possible risk of endometriosis for Seveso, Italy, residents: an assessment of exposure to dioxin. *Environ Health Perspect*. 1994 May;102(5):476-7. doi: 10.1289/ehp.94102476. Erratum in: *Environ Health Perspect* 1994 Aug;102(8):627. PMID: 8593852; PMCID: PMC1567136.
- ⁷ Hernandez-Ochoa I, Karman BN, Flaws JA (2009) The role of the aryl hydrocarbon receptor in the female reproductive system. *Biochem Pharmacol* 77(4):547–559. 10.1016/j.bcp.2008.09.037
- ⁸ Stockinger B, Di Meglio P, Gialitakis M, Duarte JH. The aryl hydrocarbon receptor: multitasking in the immune system. *Annu Rev Immunol*. 2014;32:403-32. doi: 10.1146/annurev-immunol-032713-120245. PMID: 24655296.
- ⁹ Humphrey-Johnson A, Abukalam R, Eltom SE (2015) Stability of the aryl hydrocarbon receptor and its regulated genes in the low activity variant of Hepa-1 cell line. *Toxicol Lett* 233(2):59–67. 10.1016/j.toxlet.2015.01.016
- ¹⁰ Larigot L, Juricek L, Dairou J, Coumoul X (2018) AhR signaling pathways and regulatory functions. *Biochim Open* 7:1–9. 10.1016/j.biopen.2018.05.001

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- ¹¹ Fujii-Kuriyama Y, Kawajiri K (2010) Molecular mechanisms of the physiological functions of the aryl hydrocarbon (dioxin) receptor, a multifunctional regulator that senses and responds to environmental stimuli. *Proc Jpn Acad Ser B Phys Biol Sci* 86(1):40–53. 10.2183/pjab.86.40
- ¹² Bock KW, Kohle C (2006) Ah receptor: dioxin-mediated toxic responses as hints to deregulated physiologic functions. *Biochem Pharmacol* 72(4):393–404. 10.1016/j.bcp.2006.01.017
- ¹³ Bertazzi PA, Bernucci I, Brambilla G, Consonni D, Pesatori A. The Seveso studies on early and long-term effects of dioxin exposure: a review. *Environ Health Perspect* 1998;106(Suppl 2):625-33
- ¹⁴ Rier SE, Martin DC, Bowman RE, Dmowski WP, Becker JL. Endometriosis in rhesus monkeys (*Macaca mulatta*) following chronic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Fundam Appl Toxicol.* 1993 Nov;21(4):433-41. doi: 10.1006/faat.1993.1119. PMID: 8253297.
- ¹⁵ Marinković N, Pašalić D, Ferenčak G, Gršković B, Stavljenić Rukavina A. Dioxins and human toxicity. *Arh Hig Rada Toksikol.* 2010 Dec;61(4):445-53. doi: 10.2478/10004-1254-61-2010-2024. PMID: 21183436.