REVIEW ARTICLE

Environmental factors and endometriosis

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Summary

Endometriosis represents a common gynecological condition affecting 5%-15% of childbearing age women and up to 3%-5% of post-menopausal women. This disease is defined by the presence of stromal and/or endometrial glandular epithelium implants in extra-uterine locations possibly compromising several sites. Humans and animals are daily exposed to chemical pollutants that could adversely influence physiological processes and potentially cause diseases, including endometriosis. In this review, the authors aimed at settling the influence of environmental and dietary factors on endometriosis pathogenesis. The mechanism by which dioxin and its similes (TCDD/PCBs) act changing the endometrial physiology remains uncertain and is speculative due to the difficulty in assessing the exposure over intrauterine life, childhood and adulthood and its actual consequences, in addition to the limitations to its in vitro reproducibility. We need to better understand the mechanism of action of these environmental pollutants, not only on reproductive health, but also on overall health of individuals and so prevention strategies, including not only population education, but setting exposure limits, less polluting techniques and a better use of our natural resources, could be promoted.

Keywords: Dioxins; aryl hydrocarbon receptor; tetrachlordibenzodioxin; endometriosis; diet; food habits.

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Introduction

Endometriosis

Endometriosis represents a common gynecological condition reaching 5%-15% of childbearing age women and up to 3%-5% of post-menopausal women[1]. The number of women with endometriosis is estimated to be seven million in the USA[2], being one of the main causes for gynecological hospitalization in industrialized countries[3].

This disease is defined by the presence of stromal and/or endometrial glandular epithelium implants in extrauterine location[4], possibly compromising several sites, including ovaries, peritoneum, uterosacral ligaments, retrocervical area, rectovaginal septum, rectum/sigmoid, terminal ileum, vermiform appendix, urinary bladder, and ureters[2,3,5-,7]. Some patients with endometriosis are asymptomatic; however, most of them have clinical complaints in different intensities, with the main ones being dysmenorrhea, chronic pelvic pain, infertility, deep dyspareunia, cyclic bowel and urinary symptoms, such as pain or bleeding on defecation or urination during the menstrual period. Among other factors, occasional nonspecificity of the clinical picture and the noncorrelation between symptoms and disease severity can explain the delay in endometriosis diagnosis[2,5,8-11].

A number of aspects of the disease are still study targets, with the search of the etiopathogenesis standing out, considering that if the reason for the endometriosis focus development is understood, directing efforts to improve diagnosis and treatment will be possible[12,13]. Two main etiopathogenic hypothesis lines of thought have been cited for almost one century:

- coelomic metaplasia theory, where mesothelium turns into endometrial tissue[14];
- retrograde menstruation theory, postulating the implant of endometrial cells from menstrual blood reflux through the Fallopian tubes into the abdominal cavity[15], occurring under the influence of a favorable hormone environment and immunological factors which would not clear the cells out of the inappropriate site[16,17].

Koninckx and Martin, in 1992[18], divided this disease into three distinct conditions: peritoneal, ovarian, and rectovaginal septum endometriosis, with the last one being called deep infiltrating endometriosis. In the first case, patients with peritoneal implants would be included; in the second case, the well-known ovarian cysts, typical of the disease; and in the third case, the infiltrating endometriosis affecting retrocervical and paracervical areas, in addition to gastrointestinal and genitourinary tracts.

Although the typical symptoms of endometriosis are well-known, they might be poorly specific or be related to the involvement sites of the disease foci[12,13]. Patients can experience pelvic pain, infertility, cyclic intestinal and/or urinary changes and this may not be an endometriosis case. Non-invasive endometriosis diagnosis via laboratory methods has no satisfactory results[19-22], but despite definitive diagnosis depends on surgical methods to obtain the material and disease histological confirmation, imaging methods have significantly progressed over last years, with high accuracy levels for deep endometriosis cases[23-26].

Over the last years, much has been studied about the immunological factors in endometriosis pathogenesis and many abnormalities have been found[16,27,28], with the main mechanism assessed being additional to the retrograde menstruation theory. For some reason that is uncertain at the moment, endometrial cells that enter the abdominal cavity would not be cleared and, thus, they would be allowed to implant and the disease would be developed[29].

The cells falling into endometrial cavity should be identified as antigens and undergo local immune response. Some cells, such as the macrophages, work as antigen-presenting cells to T cells through the major histocompatibility complex (MHC). MHC can be class I or II; in the first case, it attracts cytotoxic T cells and, in the second case, helper T cells. Cytotoxic cells secrete lethal substances causing the target-cell death, whereas helper T cells secrete cytokines that can lead to cell death[30]. Changes in any of the above phases can be related to endometriosis genesis[29].

Exposure to environmental factors

Humans and animals are daily exposed to chemical pollutants that can adversely influence physiological processes e potentially cause disease. Many of these environmental pollutants are persistent, having long half-lives and they can accumulate in the environment and even in living organisms and, thus, adversely influence gestational process, the children and the adult. A recent analysis by the Environmental Working Group revealed the presence of 287 different chemical agents in human umbilical cord and an important result: although not all children have been exposed to all pollutants detected, no child was exposed to no pollutants[31]. It is difficult to determine the specific or combination effect of these numerous agents on the process or disease development in specific organs, but many agents are known to be related to neoplasm development, immunological disorders, neuropsychomotor and reproductive system function changes[31].

Among numerous chemical agents identified in the human umbilical cord, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) has been widely studied because it is considered the most toxic environmental pollutant ever produced by man[32]. However, certain polychlorinated biphenyls (PCBs) have a biologic toxicity similar to TCDD and, therefore, they can act by impairing reproductive function.

PCBs have been endocrine deregulating agents widely used as dieletric fluid in transformers, capacitors, and coolers since 1930. Although PCB production has been

banned in the United States in 1976, PCBs still persist in the air, water, and soil, and it has accumulated in fatty tissue in fish, fowls, and mammals all over the world. As a result, human exposure to PCBs occurs mainly by consuming animal products and dairy foods[33].

The role of human exposure to PCBs in the development of diseases related to hormones has been addressed in several epidemiological studies since early 1990. Most endometriosis studies focus on the dioxin form (coplanar PCBs inducing biological effects through an aromatic hydrocarbon receptor binding), but no association has been found[33].

Whereas TCDD has been unwittingly introduced into our environment as a product resulting from industrial and incineration processes, PCBs have been widely applied and they were produced indiscriminately until they were banned worldwide in the 80s. These organochlorines are exceedingly resistant to degradation and, as they are lipophilic in nature, they accumulate and enhance in the food chain[33,34].

In this review, we will try to explain the complexity and the challenges of determining the potential impact of exposure to these agents with a focus on endometriosis.

Review methods

A wide MEDLINE (1966-2010) and PubMed (1966-2010) review was performed by using the following search terms:

1. *Endometriosis*
2. *Dioxin*
3. *Environmental toxins*
4. *Environmental factors*
5. *Dietary factors*

Abstracts of all selected articles were read and the manuscripts were fully reviewed. References of all articles were reviewed in search of additional information. The article selection and their review were independently performed by two reviewers (PB and SP) for quality.

Three hundred and five articles were found and, out of these, we selected those published over the last 10 years, reaching 213 articles. Out of these, we tried to select those with a relevant sample and an appropriate review, meta-analyses, and controlled studies, reaching a total of 44 articles. The selected articles were as follows: 7 systematic reviews (Recommendation Grade A – level of evidence 1A), 26 prospective and controlled studies (Recommendation Grade A – level of evidence 1B), 1 retrospective cohort (Recommendation Grade B – level of evidence 2B), 1 case report (Recommendation Grade C – level of evidence 4), 2 ecological studies (Recommendation Grade B – level of evidence 2C), and 7 simple reviews (Recommendation Grade B – level of evidence 3A). Following, after an article reference review, we selected 6 additional studies performed more than 10 years ago, but relevant for our review, as they are pioneering studies.

PCBs and endometriosis

Although the accurate endometriosis etiology remains uncertain, the mechanism of retrograde menstruation[15] seems to be the most plausible hypothesis. However, as retrograde menstruation is a common event in women without endometriosis, some other mechanism, whether it is immunological or toxic, must act to allow endometrial cells to implant into the cavity. Because of the recognized ability of PCBs to change endometrial function either in animals or humans, it is not surprising the action of these pollutants on the disease etiopathogenesis was considered as related. However, as contamination might be found in food, it could be difficult to exclude other exposure sources from food or water even in a controlled study.

Although the hypothesis has been firstly reported almost 20 years ago[35], studies trying to prove TCDD or PCB effect on the disease genesis are conflicting. Fasting prior to the collect for serum PCB measurement is known to produce false results and lactation is the main PCB excretion route; however, few studies get a strict serum sample collect with serum lipid correction and taking into account breast feeding in the analyses[36,37]. In addition, different statistical analyses and different regions (urban/rural) studied could have contributed to discrepancies in the results.

Yet we will list the main effects assigned to PCBs/TCDD, making them possible contributors to endometriosis onset.

Endometrial action

PCBs/TCDD can bind to receptors (AhR), forming heterodimeric complexes binding to xenobiotic response elements and change the expression of genes influenced by these elements. AhR receptor is an activated ligand transcription factor commonly reported as an orphan nuclear receptor, since the endogenous ligand is not known. In the non-bound form, AhR is present in the cytosol as a multiprotein complex associated with chaperon proteins. These receptors (AhR) are still known to be abundant in endometrium and immune system cells[38]. In an endometrial culture model[39], even ephemeral endometrial tissue exposure to TCDD was observed to promote increased secretion of matrix metaloproteinases (MMPs), though in the presence of progesterone, which normally would suppress the expression of these enzymes.

Because of the powerful anti-inflammatory effect of progesterone, reduced sensitivity to this steroid could contribute to the autoimmune nature of endometriosis, as well as to more specific local and systemic changes. However, only recently this loss of endometrial sensitivity to progesterone was recognized as a potential causal factor for endometriosis. Over the menstrual cycle, as progesterone levels fall into the secretory phase, increased proinflammatory cytokines and chemokines and MMPs are seen, in preparation for the high inflammatory process of menstruation[39,40].

Furthermore, these PCBs/TCDD + AhR complexes can activate proinflammatory cytokine and chemokine genes, such as IL-1, IL-8, TNF-a, and RANTES, potentially affording a chronic pattern of proinflammatory signaling and bringing on cessation of the normal endometrial function. TCDD combination to 17b-estradiol is known to further potentiate the proinflammatory effect, raising the presence of RANTES and MIP-1a (macrophage protein 1-alpha), entailing the ability to invade stromal endometrial cells and express MMP-2 and MMP-9 in them[41].

Dietary factors

Today we know some diseases are certainly influenced by diet (insulin resistance, hypertension, gall bladder disease, celiac disease, etc.)[42]. Most recommendations by associations and societies related to endometriosis are known to be made based on case reports and personal experiences.

There are several plausible theories linking diet to endometriosis and dysmenorrhea. Prostaglandin release seems to be a pathogenic factor for both endometriosis and dysmenorrhea. Diet fatty acids are prostaglandin precursors. PGE2 and PGF2 are proinflammatory n6 fatty acid metabolites, possibly increasing uterine contraction and painful symptoms. However, PGE3 and PGE3a are n3 fatty acid derivatives which are less potent in their inflammatory function; thus, they can reduce painful symptoms. N3 fatty acids are mainly found in marine oils, whereas n6 fatty acids are found in vegetable oils[43].

Endometriosis is an estrogen-dependent disease. A relationship between diet and other estrogen-dependent diseases has already been shown[44,45]. Fiber intake can increase estrogen excretion[46,47] and could, thus, play an inverse role in endometriosis risk; fat intake could reduce serum estrogen levels. A vegetarian diet would supposedly raise serum ligand and sex hormone carrier protein levels, thus reducing the available estrogen concentration[48].

In a Cochrane review, Yap et al.[49] could find vitamin B complex and magnesium intake, as well as omega 3 supplements, can exert an anti-inflammatory role in patients with endometriosis. Omega 3 and 6 fatty acids were proposed as possibilities to improve pain symptoms related to endometriosis by modulating the biosynthesis and prostaglandin biochemical activity related to pelvic pain. Likewise, magnesium and vitamins B are related to anti-inflammatory prostaglandins production and miometrial relaxation. Moreover, diet based on vegetables, vitamins, omega 3 and magnesium ultimately reduces animal protein intake and therefore reduces the excess of body fat and estrogen peripheral production[50].

However, up to this point, there is not sufficient evidence from controlled studies so that appropriate conclusions can be drawn whether or not using diets as preventive or adjuvant factors in endometriosis treatment.

Conclusion

The mechanism by which dioxin and its similes (TCDD/PCBs) act on endometrial physiology changes remains uncertain and speculative because it is difficult to assess the exposure in intrauterine life, in childhood and adulthood, as well as its real consequences, in addition to the limitations of its in vitro reproduction. In order to observe and determine the possible role of any environmental pollutants, a number of groups has performed in vitro and in vivo techniques aiming to find the cell mechanisms of the disease onset.

Studies assessing the time and degree of exposure, age group and exposure to concomitant factors should be conducted to determine how all of these factors could contribute to endometriosis genesis.

Ultimately, we should better understand the mechanism of action of these environmental pollutants not only on reproductive health, but also on the general health of the individual to promote prevention strategies which should include not only population education, but establishing limits of exposure, less polluting techniques and a better use of our natural resources.

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