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The effect of endocrine disruptors on endometrial cells: A Systematic Review

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Abstract
Endocrine disruptor plays a role as natural hormones in the body like estrogens or androgens, or thyroid hormones. It may act as the interaction of natural hormones with their receptor, or bind to a receptor and prevent the endogenous hormone from binding with their receptors. Endometrial tissue finds in uterus has gland, cells, and connective tissue. This tissue prepares the uterus for ovulation. The objectives of this review were to identify the effect of endocrine disruptors on endometrial cells. Electronic searches of literature were performed. From 38 titles, Full-text versions of the 15 identified titles were obtained and evaluated independently by two reviewers 8 of the full-text articles were excluded based on the established criteria. This process identified 7 articles for inclusion and data extraction. According the existing literatures, this study concluded that endocrine disruptors can affect on endometrial cells by regulate the expression of decidualization genes. But it can also cause endometrial dysfunction, disrupt vascular development and play important roles in tumorigenesis. The existing literatures reporting on this are small in volume and can be considered of generally low quality.
Keyword: *Endocrine, Disruptors, Endometrial Cells, Endometrial Decidualization, Bisphenol A.*

1. Introduction and Literature Review

1.1 Endocrine System and Hormone.

The body function controlled by communication between various parts and organs, this communication maintains by two system: the nervous system, and the hormonal system. Also, the endocrine system has a continuous reaction with other main communication systems of body, the nervous system, and the immune system, so any error of the endocrine system may impact these other systems (Demeneix et al., 2019). Hormones are molecules produced by endocrine glands, the interaction between the hormones and its receptor produce a cascade of biochemical reactions in the target cell that produce modification on the cell's function or activity (Hiller-Sturmhöfel & Bartke, 1998). The endocrine system regulates physiological systems: growth of the skeleton and muscles, reproduction, control of body temperature, brain development, and brain activity (Demeneix et al., 2019).The concept of endocrine function was expanded to paracrine, autocrine, juxtacrine, and intracrine functions, instead of the classic endocrine system, which has the traditional endocrine axes (Chrousos, 2007).

1.2 Endocrine Distruption.

Large numbers and large quantities of man-made chemicals present in the environment since World War II that are potentially capable of modulating and/or disrupting the endocrine system, this chemical called endocrine disruptors (Colborn et al., 1994) .Endocrine disrupter is asubstance or mixture that distrupt function of the endocrine system and causes defect on health in an intact organism, or populations." (WHO | World Health Organization, 2002). Another definition is exogenous agents that interfere with the synthesis and actionof endocrine hormones that are affect on the maintenance of development of human body (Markey et al., 2002)

There is many Man-made chemicals have been reported to act as hormone mimics include: organochlorine pesticides (DDT and its metabolites, endosulfan, toxaphene, β-HCH, and dieldrin), polychlorinated biphenyls (PCBs; both mixtures and individual congeners) and their hydroxylated metabolites, dioxin-like chemicals (PCDDs and PCDFs), bisphenol-A (a chemical used in the manufacture of polycarbonate-derived products and epoxy resins), alkylphenolic chemicals (products of the degradation of industrial surfactants and antioxidants), vinclozolin (a fungicide), tributyl tin (TBT; an anti-fouling compound) and a few phthalates (widely used as plasticizers) (Tyler et al., 1998).

Endocrine disruptor plays a role as natural hormones in the body like estrogens or androgens, or thyroid hormones. It may act as the interaction of natural hormones with their receptor, or bind to a receptor and prevent the endogenous hormone from binding. Such as chemicals that prevent hormones are anti-estrogens and anti-androgens. This interference produces adverse developmental, reproductive, neurological, and immune effects in both humans and wildlife (Monneret, 2017).

1.3 Endometrial Cells.

Endometrial tissue finds in uterus has gland, cells, and connective tissue. This tissue prepares the uterus for ovulation. Normal endometrial cells mustn't find after menopause, when these endometrial cells grow abnormally or spread to other organs of the body so, it become tumors. This can detect by endometrial biopsy. This cancer that starts in the inner layer of uterus called endometrial cancer. In this study report that the shedding of normal endometrial cells by women who are postmenopausal indication for abnormal finding that may be because of presence of endometrial carcinoma(Gomez-Fernandez et al., 2000). In other study reported about accuracy of endometrial biopsy in diagnosis of endometrial cancers, that concluded this type of biopsy has high accuracy in diagnosis of endometrial cancer (Clark et al., 2002).

1.4 Effect of endocrine disruptors on endometrial Cells.

All organs of body that controlled by hormones can affected by endocrine disruptors. So, the endocrine disruptors can be associated with disability, deformity, sexual development and brain problems. The living environment determines the number of endocrine disruptors. And these EDs contribute as important factor for woman organ disorders (la Rocca et al., 2015). The carcinogenic effects of endocrine disruptors are reasonable, but their mechanisms unclear (Mallozzi et al., 2017).

1.5 Endometrial Decidualization and Bisphenol A.

Bisphenol A (BPA) is a common endocrine disruptor exposed human life, from prenatal to adult age. Endometrial decidualization is aprocess of pregnancy, with which the uterus prepares for embryo implantation. Decidualization of endometrial stromal cells is important for successful pregnancy and outcomes (Gellersen & Brosens, 2014).

Materials and Methods

Search Strategy

This systematic review was intended to identify the effect of endocrine disruption on endometrial cells. Key words were chosen to include endocrine, disruptors, and endometrial cells.

A Medline (PubMed) search was undertaken to identify randomized controlled trials, systematic review, cohort studies and case series.

Selection of Studies

Two of the authors independently screened the titles and abstracts obtained from the electronic search for inclusion or exclusion. Disagreements were resolved via direct discussion. Full-text versions of articles were obtained when compliance with the criteria required for the review was positive or when exclusion could not be confirmed.

Five reviewers independently per formed a review of the full-text articles and disagreements were again managed via reviewer discussion prior to final inclusion or exclusion. The search protocol is summarized in Table 1.

Excluded Studies

Criteria for exclusion included:

- Failure to identify the inclusion criteria
- Non-English language

Included Studies

Criteria for inclusion included:

- Published last 10 years
- Controlled clinical trials and Cohort Studies
- Systematic Review
- Case Report
- Humans and animals

Statistical Analysis

The literature identified in this review does not meet criteria required for quantitative data or meta-analysis. Further, the heterogeneity of the case series prevents the plotting of outcomes to feature results.

Results

The Medline (PubMed) search identified 38 titles,23 were excluded with author agreement subsequent to title, abstract review.

Full-text versions of the 15 identified titles were obtained and evaluated independently by two reviewers 8 of the full-text articles were excluded based on the established criteria. This process identified 7 articles for inclusion and data extraction. The characteristic of included studies summarized in table 2.

Table 1 Systematic Search Strategy

Focus question:	What is the effect of endocrine disruptors on endometrial cells?
Search strategy	(endometrial cell) AND (endocrine disruptor)
Database search	
Language	English
Electronic	PubMed (Medline)
Selection criteria	
Inclusion criteria	• Published last 10 years • Controlled clinical trials and Cohort Studies • Systematic Review • Case Report • Humans and animals
Exclusion criteria	• Failure to identify the inclusion criteria • Non-English language

Table 2 Characteristic of Included Studies

Name	Aim of study	Total number of patient	Treatment outcome
(Xiong et al., 2020)	Determine the correlation between environmentally relevant levels of Bisphenol exposure and histone modification during endometrial stromal cells decidualization. B	6 patients (aged 40–47 years) with regular menstrual cycle, who underwent surgery for early stage of cervical cancer.	This study provides that BPA exposure can regulate the expression of decidualization-related genes by affecting histone modification, impairing endometrial decidualization.
(Aldad et al., 2011)	Evaluate the effect of bisphenol-A (BPA), a xenoestrogen endocrine disruptor, on endometrial P receptor (PR) expression in nonhuman primates and human cells.	10 adult female African green monkeys	Bisphenol-A play a role as a weak estrogen. However, when administered with E2, BPA diminishes E2-induced PR expression. The estrogen-like effect of BPA reported in exposed humans may be mediated by PR blockade and a resultant decrease in the estrogen inhibition normally imparted by P. Diminished PR expression may underlie previous reports linking BPA exposure to endometrial dysfunction in humans.
(Helmestam et al., 2014)	Evaluate Bisphenol A effects on human endometrial endothelial cell angiogenic activity	five premenopausal women with regular menstrual cycles, who underwent hysterectomy for benign medical conditions	Bisphenol disturb endometrial vascular development and function, and subsequently endometrial actions important for normal function and successful implantation and placentation.
(Reed et al., 2018)	Identifyhormonally-regulated miRs in endometrial stromal cells and to investigate the effects of BPA on selected miRs	females 77 (18-45 years old) undergoing hysterectomy for benign conditions	BPA and E2 downregulate miR-27b thereby leading to upregulation of genes important for vascularization and angiogenesis of the endometrium during the menstrual cycle and decidualization.
(Mannelli et al., 2015)	Examined the potential effects of an ED, bisphenol A (BPA), on endometrial maturation/decidualization, receptivity and secretion of decidual factors (biomarkers).	6 hysterectomy specimens from different donors	The multi-targeted disruption of BPA on decidual cells, at concentrations commonly detected in the human population, raises great concern about the possible consequences of exposure to BPA on the function of decidua and thus its potential deleterious effect on pregnancy.
(Chou et al., 2017)	Investigated whether BPA exposure can disrupt miRNA regulation and its gene expression regarding to EC carcinogenic progress.	-	miRNAs when underlying BPA exposure may play important roles in tumorigenesis.
(Yao et al., 2021)	Evaluate the mechanism underlying adverse effects of ZEA in human decidual stromal cells and suggests RSV a potential therapeutic candidate to alleviate ZEA-induced cytotoxicity during decidualization.	-	Clinical strategies to relief negative effects of endocrine disruptor by applying RSV during decidualization, especially for women in preparation of getting pregnant.

Conclusion

According the existing literatures, this study concluded that endocrine disruptors can affect on endometrial cells by regulate the expression of decidualization genes. But it can also cause endometrial dysfunction, disrupt vascular development and play important roles in tumorigenesis.

Recommendation

The existing literatures reporting on this are small in volume and can be considered of generally low quality. So, there is need for research comparing between presence or absence of endocrine disruptors and its directly affect positively or negatively in endometrial cells.

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