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Review article

Impact of endocrine disrupting chemicals on onset and development of female reproductive disorders and hormone-related cancer

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ABSTRACT

A growing body of evidence suggests that exposure to chemical substances designated as endocrine disrupting chemicals (EDCs) due to their ability to disturb endocrine (hormonal) activity in humans and animals, may contribute to problems with fertility, pregnancy, and other aspects of reproduction. The presence of EDCs has already been associated with reproductive malfunction in wildlife species, but it remains difficult to prove causal relationships between the presence of EDCs and specific reproductive problems *in vivo*, especially in females. On the other hand, the increasing number of experiments with laboratory animals and *in vitro* research indicate the ability of different EDCs to influence the normal function of female reproductive system, and even their association with cancer development or progression. Research shows that EDCs may pose the greatest risk during prenatal and early postnatal development when organ and neural systems are forming. In this review article, we aim to point out a possible contribution of EDCs to the onset and development of female reproductive disorders and endocrine-related cancers with regard to the period of exposure to EDCs and affected endpoints (organs or processes).

Contents

1. Introduction

Human reproduction presents a complex chain of interdependent events, many of which can be disturbed by exogenous agents.

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Declining conception rates and high incidence of female reproductive disorders over the past half century suggested by numerous studies [1–4] is attributable to cultural changes (e.g. delayed childbearing, increased contraception in women), but exposure (of the fetus, mother or father) to endocrine disrupting compounds (EDCs) may also contribute. Several definitions of EDCs exist, the International Programme on Chemical Safety (IPCS, 2002) [5] defines endocrine disruptor as an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations. A wide variety of natural (phytoestrogens) or synthetic chemical compounds, including pharmaceutical drugs (diethylstilbestrol; DES), pesticides (DTT, atrazine, methoxychlor; MXC), polychlorinated biphenyls (PCBs), dioxin and dioxin-like compounds, plastics (bisphenol A; BPA) and plasticizers (phthalates), and heavy metals (lead, arsenic, aluminum, cadmium) have been recognized to possess endocrine disrupting activity. It is well established that EDCs may act primarily through binding to nuclear hormone receptors exerting agonistic or antagonistic effects leading to alteration of transcription of target genes (genomic pathway). Currently it is known that EDCs' effects may occur through binding to membrane steroid hormone receptors or G protein-coupled protein (GPR30) resulting in rapid downstream intracellular signaling and/or regulation of gene transcription [6] (Fig. 1). Many of the reported effects of EDCs are caused through alteration of estrogen signaling, probably because it is evolutionarily conserved among animals and is crucial for proper ontogeny and function of multiple female reproductive organs [7]. Recent studies provide new insights into other mechanisms, such as oxidative stress [8], genetic susceptibility [9,10], and epigenetic effects [11,12], related to EDCs' involvement with detrimental reproductive health outcomes (Fig. 1). The scientific knowledge about the potential adverse health effects of EDCs in humans and wildlife is summarized in a document published in 2013 by World Health Organization (WHO) and the United Nations Environment Programme (UNEP) [5] and in The Endocrine Society's second Scientific Statement [13].

Despite the examples of unambiguous effects of EDCs on wildlife [5,13], it remains difficult to prove causal relationships between the presence of EDCs and specific reproductive problems *in vivo*, especially in females. In males, poor semen quality and testicular cancer are measurable and increasing [14,15]; in contrast, changes in oocyte quantity and quality are difficult to measure because of differences in male and female gametogenesis and the fact that female organs and their function are largely inaccessible. Cellular models and animal toxicological studies have demonstrated that EDCs may have detrimental effects on female reproduction. In humans, there is a growing number of epidemiological studies about EDCs and adverse impact on reproductive function. Given that the reproductive physiology of humans and other mammals is remarkably similar, it is reasonable to predict that human female reproductive disruption can occur after exposure to EDCs (Fig. 2). A number of human epidemiological studies support these assumptions. Several occupational exposures have been related to increased risk of adverse effects on reproductive health and reduced fertility in females [13]. Biomonitoring studies have identified presence of EDCs during different developmental stages, in adults, children, pregnant women, and fetuses. Because many EDCs show a non-monotonic dose-response relationship, even exposure at low doses may be linked to adverse reproductive health effects [5,13]. Moreover, humans and animals are exposed to continuously varying mixtures of EDCs, which can influence each other's actions in an additive, antagonistic or synergistic way. The harmful dose of EDC mixtures is significantly lower than for any EDC [5,13]. Very little is known about the reproductive health risks associated with EDC mixtures. The study of different aspects of endocrine disruption in humans is complicated by challenges concisely summarized by Fudvoye et al. [16]: 1) *variable persistence* of EDCs in the body and the environment, 2) various effects depending on the *critical periods*

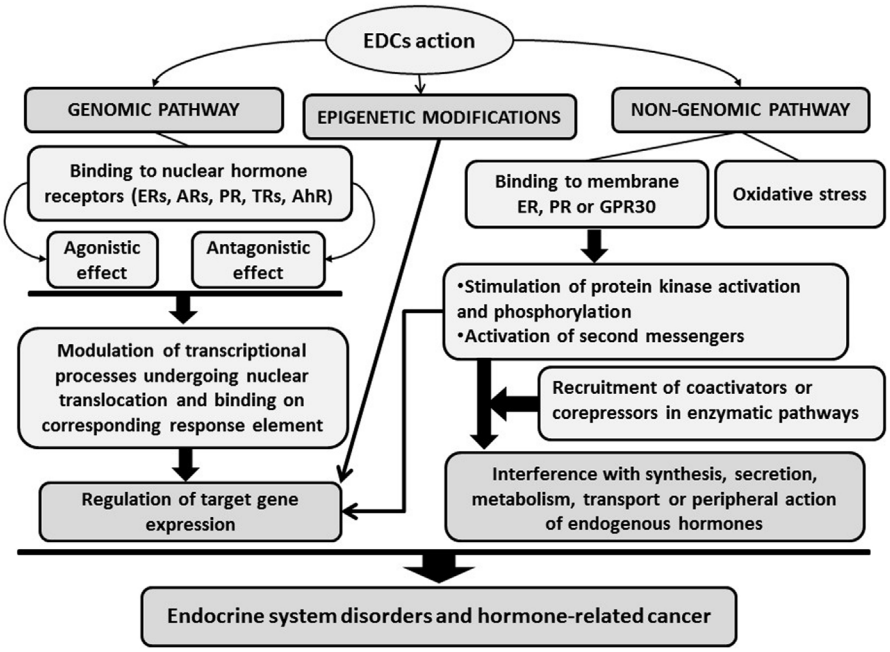

Fig. 1. Potential mechanism(s) of endocrine disrupting chemicals (EDCs) action. In the "genomic pathway", many actions of EDCs are mediated by the classical nuclear hormone receptors (NRs), especially estrogen (ERs), androgen (AR), progesterone (PR) receptors, and the orphan aryl-hydrocarbon receptor (AhR). After binding to NRs, EDCs can affect the transcription of target genes in the nucleus by binding to corresponding response element (RE) of target genes. The "non-genomic pathway" of EDCs action may occur through membrane steroid receptors (ER, PR) or G protein-coupled receptor (GPR30) leading to rapid downstream intracellular signaling or directly alteration of the transcription of target genes.