Polycystic ovary syndrome and environmental toxins

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Polycystic ovary syndrome (PCOS) is the most common, heterogeneous, and multifactorial endocrine disorder in premenopausal women. The pathophysiology of this endocrinopathy is still unclear; however, the heterogeneity of its features within ethnic races, geographic location, and families suggests that environment and lifestyle are of prime importance. This work is mainly focused on the possible role of the most common and studied environmental toxins for this syndrome in the pathogenesis of PCOS. Plasticizers, such as bisphenol A (BPA) or phthalates, which belong to the categories of endocrine disrupting chemicals (EDCs) and advanced glycation end products (AGEs), affect humans' health in everyday, industrialized life; therefore special attention should be paid to such exposure. Timing of exposure to EDCs is crucial for the intensity of adverse health effects. It is now evident that fetuses, infants, and/or young children are the most susceptible groups, especially in the early development periods. Prenatal exposure to EDCs that mimic endogenous hormones may contribute to the altered fetal programming and in consequence lead to PCOS and other adverse health effects, potentially transgenerationally. Acute or prolonged exposure to EDCs and AGEs through different life cycle stages may result in destabilization of the hormonal homeostasis and lead to disruption of reproductive functions. They may also interfere with metabolic alterations such as obesity, insulin resistance, and compensatory hyperinsulinemia that can exacerbate the PCOS phenotype and contribute to PCOS consequences such as type 2 diabetes and cardiovascular disease. Since wide exposure to environmental toxins and their role in the pathophysiology of PCOS are supported by extensive data derived from diverse scientific models, protective strategies and strong recommendations should be considered to reduce human exposure to protect present and future generations from their adverse health effects. (Fertil Steril® 2016;106:948–58. ©2016 by American Society for Reproductive Medicine.)

Key Words: Polycystic ovary syndrome, endocrine disrupting chemicals, bisphenol A, advanced glycation end products

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POLYCYSTIC OVARY SYNDROME DEFINITION

Polycystic ovary syndrome (PCOS) is the most common, complex, and heterogeneous endocrine disorder in women of reproductive age (1). Its prevalence is estimated to be between 5% and 10% and even up to 21%, depending on the diagnostic criteria and geographic location (2–5).

PCOS is characterized by great diversity of its clinical presentation of reproductive dysfunction and metabolic abnormalities (6). Hyperandrogenism is a key feature of this endocrinopathy that contributes to clinical phenotypes and fertility dysregulation (7). The most common sequelae of hyperandrogenism in the setting of the PCOS phenotype are hirsutism and acne as well as also alopecia (1, 8). The hormonal and metabolic alterations may result in reproductive disruption, including menstrual cycle dysfunction, chronic anovulation, and infertility (9). The majority of women with PCOS have insulin resistance (10, 11), which may lead to the development of obesity (12). Its prevalence, however, rises with the increasing rate of obesity (13). PCOS is characterized by central adiposity (14, 15) and the profile of metabolic disturbances similar to those seen in the metabolic syndrome (16), such as atherogenic dyslipidemia (high serum triglycerides and LDL-cholesterol levels, low HDL-cholesterol levels) (17–19) and impaired glucose tolerance, which very often lead to the development of type 2 diabetes (T2DM) (20). Patients with PCOS are also characterized by higher blood pressure values and increased thrombotic activity and several cardiovascular as well as insulin resistance markers (21, 22).

The pathophysiology of this endocrinopathy is still unclear; however, the heterogeneity of its features suggests that genetic as well as environmental factors and lifestyle are of scientific and clinical importance (9, 23, 24).

Received August 5, 2016; revised and accepted August 15, 2016; published online August 22, 2016.
A.Z.R. has nothing to disclose. E.D.-K. has nothing to disclose.
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Fertility and Sterility® Vol. 106, No. 4, September 15, 2016 0015-0282/$36.00
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http://dx.doi.org/10.1016/j.fertnstert.2016.08.031

This work mainly focuses on the possible role in the pathogenesis of PCOS of common environmental toxins. Plasticizers such as bisphenol A (BPA) or phthalates and advanced glycation end products (AGEs) affect human health in everyday life, and, therefore, special attention to such exposures should be paid, as they may lead to adverse health outcomes in women throughout their life cycle.

ENVIRONMENTAL FACTORS—THE SIDE EFFECTS OF CIVILIZATION

Endocrine Disrupting Chemicals

Endocrine disrupting chemicals (EDCs) or endocrine disruptors are "exogenous substances or mixtures that alter function(s) of the endocrine system and consequently cause adverse effects in an intact organism or its progeny or (sub) populations" (25). Currently, nearly 800 chemicals are known or suspected to play a negative role in hormonal disruption, and this list is rapidly growing (26). It is a heterogeneous group of molecules with the high potential to interact directly with hormone receptors (e.g., estrogen, androgen, thyroid, or P) as agonists or antagonists, triggering different molecular pathways. Some EDCs can also impact proteins involved in the transport of hormones, such as sex hormone–binding globulin (SHBG), and thus disrupt the delivery of endogenous hormones to target cells (27–29). Their molecular structure usually consists of a phenol group and may possess halogen group substitution by chlorine and bromine; therefore, they can easily mimic steroid hormones and "interfere with the synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction and developmental process" (definition of the U.S. Environmental Protection Agency, EPA) (30). Thus, they have been considered among strong risk factors in the development of obesity, metabolic disorders, infertility, endocrinopathies, diabetes, and hormone-dependent cancers (breast, endometrial, and prostate neoplasms) globally (2, 3, 8, 11, 17, 21).

Although the data about direct adverse health effects after human exposure to EDCs are still limited, abundant evidence from in vitro and animal studies, as well as from wildlife observations, are sufficiently alarming that several professional organizations have issued statements about a call to action (26, 31). Over the last two decades, concerns about EDC safety for humans have become increasingly more supported with new scientific and clinical data. Although the mechanisms of EDCs actions in humans are still not well understood and are controversial, there are some emerging issues of concern such as their affinities for hormone receptors, binding proteins, concentrations, and duration as well as timing of EDC exposures that can determine their health impact.

The affinity of the hormone receptors for the EDCs is usually much lower than for natural ligands. For example, the affinity of the classical estrogen receptors (ER), ER-α and ER-β, to one of the most commonly used EDCs, BPA, is 1,000–10,000 fold lower than for 17β-estradiol (E_2) (32). However, EDCs can act in several tissues, even in low doses, also below the level of exposure at which no adverse effects in organism have been observed by toxicologists (33, 34). Thus, long-term exposure of humans even to EDCs levels below the estimated tolerable daily intake dose may be not as safe as previously considered. Moreover, the timing of EDC exposure during the lifespan seems to be crucial for the severity of biological effects, as younger organisms are more sensitive and more susceptible to EDCs' action. In addition, children can have even higher exposures to EDCs especially through their hand-to-mouth activity.

Humans are exposed in daily life to a mixture of different EDCs in a variety of concentrations. The biological effects of exposure to such a cocktail of chemicals are difficult to estimate as the toxicity of such substances is usually tested for single chemicals, not mixtures (22). The predictability of combination effects is complex and difficult as it depends on the endocrine potency of different EDCs in the mixture, their concentration, and the metabolic rate of the exposed individual. The liver plays an essential role in EDCs metabolism and their excretion. The most important liver enzyme is uridine diphosphate-glucuronosyl transferase (UDP GT) (35). Some observations suggest different mechanisms of EDC metabolism depending on gender (36).

The molecular structure and lipophilic properties of some EDCs may promote their bioaccumulation in the adipose tissue of animals and humans (37). EDCs have been detected also in biological fluids such as sera (38), urine (35), amniotic fluid (39), and breast milk (40). Some EDCs persist in the body for a long time, such as persistent organic pollutants (POPs), and some (e.g., pesticides) are quickly metabolized and cleared from the organism, although chronic exposure can lead to bioaccumulation (37, 41). Nevertheless, the presence of EDCs in amniotic fluid and placenta is alarming, as EDCs can alter the normal hormonal control of fetal development (42).

Advanced Glycation End Products

Advanced glycation end products (AGEs), also called glycotoxins, are proinflammatory molecules that either are derived from nonenzymatic glycation and oxidation of proteins and lipids (Maillard reaction) or are absorbed from exogenous sources (43, 44). Despite the type of exposure, all AGEs can interact with cell surface receptors called RAGE (receptor for AGEs), which act as signal transduction receptors triggering activation of proinflammatory conditions (45–49) and oxidative stress (46, 50, 51). Therefore, they are described to take part in aging, diabetes, atherosclerosis, female fertility, and a variety of cancers (51).

Dietary and Environmental Exposure to EDCs and AGEs

Over the last two decades, globalization and consumerism have led to increased human exposure to anthropogenic chemicals and glycotoxins. Some EDCs such as POPs (e.g., polychlorinated biphenyls [PCB], hexachlorobenzene [HCB], dichlorodiphenyltrichloroethane) are persistent in the environment and possess a high potential for

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