Environmental determinants of polycystic ovary syndrome

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In this review, we summarize existing research on a variety of environmental factors potentially involved in the etiology, prevalence, and modulation of polycystic ovary syndrome (PCOS), and we suggest avenues for future research. The main environmental factors we consider include environmental toxins, diet and nutrition, socioeconomic status, and geography. There is some evidence that environmental toxins play a role in disrupting reproductive health, but there is limited research as to how these toxins may affect the development of PCOS. Although research has also shown that PCOS symptoms are reduced with certain dietary supplements and with weight loss among obese women, additional research is needed to compare various approaches to weight loss, as well as nutritional factors that may play a role in preventing or mitigating the development of PCOS. Limited studies indicate some association of low socioeconomic status with certain PCOS phenotypes, and future research should consider socioeconomic conditions during childhood or adolescence that may be more relevant to the developmental onset of PCOS. Finally, the limited scope of comparable international studies on PCOS needs to be addressed, because global patterns of PCOS are potentially valuable indicators of cultural, environmental, and genetic factors that may contribute to excess risk in certain regions of the world. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)

Key Words: PCOS, polycystic ovary syndrome, environment, toxins, socioeconomic, diet

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Recent reviews of polycystic ovary syndrome (PCOS) research have found that genetic susceptibility has been associated with PCOS, and that the environment is likely to play an important role in the expression of those genetic traits (1, 2). Environmental risk factors may include exposure to harmful conditions throughout life that trigger or exacerbate the pathology of PCOS (3). In this report, we discuss specific environmental factors potentially involved in the etiology, prevalence, and modulation of the PCOS phenotype, including environmental toxins, diet and nutrition, socioeconomic status (SES), and geography.

There is a growing interest in considering PCOS pathology across the life course (2, 4–7). That is, although PCOS symptoms are often recognized in adolescence, the physiologic ramifications of the condition influence a woman throughout her life, with metabolic and hyperandrogenic signs and symptoms appearing early in life, reproductive dysfunction becoming more obvious in adulthood, and metabolic and cardiovascular risk increasing in middle and later life (5–7). To consider those environmental factors related to PCOS, it is therefore crucial to consider the timing of when these environmental insults may occur and how exposure at various stages may affect the natural progression of this disease.

Considering the early presentation of PCOS, generally during adolescence, researchers have considered potential environmental risk during the prenatal and postnatal periods. Evidence from experimental studies suggest that intrauterine exposure to excess androgens or glucocorticoids during certain critical periods of fetal development may lead to the development of PCOS symptoms as well as determine the phenotypic expression of PCOS during adulthood (2). One hypothesis is that intrauterine growth restriction (IUGR) can lead to increased prenatal exposure of androgens/glucocorticoids, which in turn may induce the fetal programming of PCOS (2, 8). The research on this

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potential pathway is mixed, with some data supporting an association between those born small for gestational age (SGA; a condition indicative of IUGR) and PCOS (8) and other data indicating no such association (9, 10).

Although evidence from human studies is lacking regarding potential prenatal environmental factors, there is more evidence that postnatal exposure to environmental risk factors are linked to PCOS. Harmful lifestyle factors, including obesity and lack of exercise have been suggested as potential environmental risk factors associated with the metabolic conditions related to PCOS (2). Obesity has been found to be related to exacerbated metabolic and ovulatory dysfunction related to PCOS (11, 12), and weight loss has been found to restore ovulation and improve hyperandrogenism (13, 14). In addition, racial/ethnic variation in phenotypes further suggests that lifestyle and cultural factors are likely to play a role in these metabolic consequences of PCOS (3). In the present report we therefore aim to outline the current research on environmental risk factors of PCOS and potential avenues for future research.

ENVIRONMENTAL TOXINS

There is a growing body of evidence that environmental toxins have a significant impact on human health and reproduction (15, 16). Environmental toxins are defined as chemical pollutants in the environment that have adverse effects on biologic organisms. These pollutants may be inhaled, absorbed through skin and mucous membranes, or ingested. Scientific evidence has emerged showing significant and lasting effects of environmental toxins on human reproductive health (17–19).

Although pollutants such as tobacco smoke, lead, pesticides, and mercury are harmful to the general population, endocrine-disrupting chemicals (EDCs) are of particular interest to reproductive health, including PCOS and its related symptoms. In 1996, the United States Environmental Protection Agency (EPA) was given a mandate under the Food Quality Protection Act and Safe Drinking Water Act to develop testing to screen for specific endocrine effects related to environmental EDCs after evidence demonstrated an association between EDCs, including environmental estrogens, antiandrogens, and chemicals such as phthalates, and decline in sperm count and cryptorchid testes among men (20, 21).

Subsequent research as a result of the EPA mandate, demonstrated EDCs present in organic wastewater, primarily in the form of human byproducts, including potent pharmaceutical products, phytosterols such as estrogens, β-blockers, antiepileptic drugs, and lipid-regulating agents (22). These organic contaminants were identified in United States streams, with the potential of contaminating the water supply (23–25). Two recent case-control studies investigated the association between concentrations of specific EDCs and PCOS (26, 27). These studies found significantly higher serum levels of perfluorinated compounds (specifically perfluorooctanoate and perfluorooctaone sulfonate), polychlorinated biphenyls (PCBs), pesticides, and polycyclic aromatic hydrocarbons among women with PCOS compared with control subjects, although a causative relationship could not be determined (26, 27). There is also evidence indicating higher serum levels of bisphenol A (BPA), a synthetic compound with mild estrogenic activity found in many common plastic consumer products, among women with PCOS compared with control subjects (28); some evidence from animal studies suggests an association between neonatal exposure to BPA and subsequent development of PCOS-like symptoms (29). Higher levels of BPA exposure can lead to elevated androgen levels, which can then lead to impaired metabolism of BPA (28, 30).

Considering the confirmed presence of these environmental contaminants in groundwater, food, air, and common household products (31), and the evidence of association with PCOS (26–28,30), future research is needed to assess the role that these EDCs may play in disrupting reproductive health among women and possibly triggering or exacerbating PCOS and its related symptoms.

Although a limited number of EDCs have been linked to reproductive health in general and to PCOS in particular, many other EDCs have yet to be considered regarding their possible role in the development of PCOS. Potential suspect EDCs that future research should consider, include additional PCBs, polychlorinated dibenzofurans, chlordecone, and dibromochloropropane, which have been found to alter pubertal development and fecundity (32–35). Other EDCs also may be considered in future studies, including those already shown to affect humans, such as 2,3,7,8-tetrachlorodibenzodioxin, methyl mercury, environmental estrogens (xenoestrogens), and dichloro-diphenyl-trichloroethane. Although many such chemicals have been banned in the United States, risk of exposure persists through lingering contaminants in the environment and the use of products from outside the United States, and their influence on PCOS and its related symptoms is unknown (32).

The industrialized food system has been recognized as a major contributor to the introduction of toxic chemicals into the environment that may influence reproductive health (36) and possibly affect the development of PCOS. While not widely recognized as "toxins," certain food sources such as starch-based and dairy foods have been found to promote exaggerated insulinogenic responses in women with PCOS (37). Gluten, found in wheat, has been identified as an endocrine disruptor increasing prolactin in children and adolescents with celiac disease (38). The mechanism by which grains alter the endocrine system may be through their inherent phytoestrogen production (39) or from agricultural pesticides found to interact with thyroid, androgen, and estrogen pathways (40). Dairy products from lactating cows may affect estrogen and testosterone levels as well as insulin resistance from the milk itself or potentially from hormones administered to animals (41). In general, milk proteins have insulinotropic properties, but the whey component is the predominant influence on insulin secretion (42, 43). Whey protein is an estrogenic endocrine disruptor present in many sports nutritional supplements (44). The insulinogenic property of whey protein could exacerbate hyperinsulinemia and, subsequently, hyperandrogenism in women with PCOS. Avoidance of starch-based foods and dairy has been shown to reduce obesity and insulin resistance, resulting in decreased hyperandrogenism in women with PCOS (45). In contrast, increased consumption of vitamin D and