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Review Article

Exploring the connection: endocrine disruptors and polycystic ovarian syndrome

M. Shakir Hussain*, Ajit Kumar Mishra

Department of Pharmacology, King George's Medical University, Lucknow, Uttar Pradesh, India

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***Correspondence:**
Dr. M. Shakir Hussain,
Email: msh30091989@gmail.com

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ABSTRACT

Polycystic ovarian syndrome (PCOS) is heterogeneous endocrine disorder in females manifesting reproductive dysfunction and metabolic abnormalities. Endocrinopathy in the form of hyperandrogenism leading to alteration in clinical phenotype and fertility seen. Atherogenic dyslipidaemia and insulin resistance as a result of metabolic disturbance also encountered. Recent years, endocrine disrupting chemicals (EDCs) are widely studied and linked for their alleged role in the development of PCOS. EDCs like bisphenol A (BPA), Phthalate, methoxychlor and chlorpyrifos which are present in many industrial as well as daily use products poses risk of development of various diseases. This review discusses the role of EDCS specially BPA in the pathogenesis of PCOS with study of interest identified and extracted from databases like Pub Med and Google scholars using MeSH keywords. BPA has estrogenic property and binds to oestrogen receptors α and β. Stimulation of ovarian theca cells and dysregulation of steroid biosynthesis leads to androgen overproduction. It stimulates GnRH Pulse generator, decreasing the level of LH hence fertility is affected. BPA also interact with adipose tissue receptors and causes differentiation, lipid deposition and inhibition of adiponectin. Its serum and urinary levels are found to be elevated in PCOS patient. In animal studies, it is found that BPA exposure causes impaired folliculogenesis, insulin resistance and DNA methylation. EDC exposure, especially BPA which is an integral constituent of many industrial and daily use items may cause PCOS possibly by altering androgen synthesis, adipocyte stimulation and epigenetic modification.

Keywords: Endocrine disrupting substance, BPA, PCOS

INTRODUCTION

Environmental protection agency (EPA) USA define EDAs as ''exogenous agents that 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 processes.' The heterogenic group of chemicals known as EDs includes both natural and synthetic molecules. Due to their phenolic structure, EDs frequently interfere with the synthesis of steroid hormones and interact with their receptors. This may therefore frequently result in the emergence of numerous metabolic diseases or even hormone dependent malignancies (i.e. breast, uterine or prostate cancer).[1] Pesticides, plasticizers, industrial by-products, contaminants, and other compounds are all included in ED. Polychlorinated biphenyls (PCB), phthalates, dioxins, and BPA are the most prominent.[2] These substances have a tendency to bio accumulate in the adipose tissue of all living organisms because of their lipophilic structure. Humans are at the end of the food chain, thus they are exposed to the highest doses of these compounds.[3] EDs have been found in biological fluids such serum, urine,

milk, and amniotic fluid, and human adipose tissue.[4-7] PCOS is characterized by anovulation, hyperandrogenism, polycystic ovarian morphology, metabolic dysfunction, and infertility. Additionally, this syndrome is associated with psychological and sexual disorders. It is regarded as the most prevalent and heterogeneous endocrine disorder in women of childbearing age worldwide.[8-11] These days, the Rotterdam criteria are the most popular for PCOS diagnosis. A variety of symptoms and indicators identify PCOS. The most prevalent ones, such as hirsutism, alopecia, and acne, are caused by excessive androgen production. The chin, neck, lower face, and preauricular region are areas where hair growth is most typical. The lower back, abdomen, buttocks, perineal area, inner thighs, and peri areolar area are common areas where excessive hair growth develops. Women with PCOS frequently experience ovulatory dysfunction, irregular periods, and fertility issues.[12]

Although they are not necessarily necessary for a diagnosis, insulin resistance and polycystic ovarian morphology can be signs of PCOS. When an ovary's volume is less than 10 ml or there is an increase in antral follicles, ultrasonography, which is used to examine ovarian morphology, can confirm polycystic ovarian morphology.[13] BPA-a ubiquitous environmental xenoestrogen. One of the most frequently produced compounds worldwide is BPA (46 billion pounds produced each year). a British chemist named Charles Edward Dodds identified it as an artificial oestrogen in 1930. BPA is diphenylmethane derivative formed by two phenol rings linked to two methyl groups. BPA can interact with oestrogen receptors because of its phenolic nature (ER). Thus BPA and its metabolites are frequently viewed as xenoestrogens.[14,15] Biochemical assays have confirmed its estrogenic activity via classical ER (ERa and ERb); however, its affinity is 1000-10000-fold lower than that of 17b-estradiol (E2). However, BPA shows approximately 10-fold higher affinity to ERb compared to Era.[16,17] There are also suggestions that BPA can interact with transmembrane ERs such as G protein coupled receptor.[1,8] In industry, BPA is used as a plasticizer. It is present in food packages, bottles (also baby bottles), CDs, DVDs, electronic equipment, dental sealing, carbonless receipts, eye lenses and water pipes.[1] The 95% of the human population examined had BPA found in their bodies.[18,19] This is a result of both its high daily exposure and the packaging leaks into foods. As a result, exposure to BPA primarily occurs through consumption of contaminated food and drink, as well as through skin absorption.[7,20] Due to BPA's oestrogen-like effects, ovarian cells appear to be a sensitive target for it. BPA appears to interfere with ovarian folliculo-genesis by acting through non-classical membrane oestrogen receptors, such as GPR30 and ERRg, as well as the classical ERa and ERb.[18]

LITERATURE SEARCH

The aim of the literature search was to find all studies examining the associations between BPA exposure and PCOS or reproductive problems in female. To that end, a broad search was conducted, utilizing PubMed, Google Scholar, and Web of knowledge. In PubMed, the search query "((Bisphenol A) and (Polycystic ovarian syndrome)) and ((Human) or (Animal))" was used, which resulted in 60 articles.

Literature search in PubMed with the keywords-Bisphenol A, polycystic ovarian syndrome, human, animal-resulted in 60 articles.

The criteria used to select the studies was as follows: Study subjects were environmentally (through diet, dermal exposure, dust, dental fillings, etc.) or occupationally exposed to BPA, exposure was measured by blood, urine, environmental sampling, or occupational records and human and animal *in vivo* and *vitro* studies were selected.

DISCUSSION

Complex pathogenesis of PCOS is still poorly understood. Gonadotropin-releasing hormone (GnRH) pulse generator activity is exaggerated in women with PCOS, resulting in persistent LH elevation, which impairs follicular growth and increases ovarian androgen production.[15,21]

Table 1: Association of endocrine-disrupting chemicals with PCOS in women. Studies in this review includes the following author's name.

Authors	Study design	Sample size	Outcome
Takeuchi and Tsutsumi[22]	Case-control	41	Serum BPA level higher in PCOS women and men, compared to healthy women
Takeuchi et al[23]	Case control	73	In all subjects, increased serum BPA was positively correlated with androstenedione, and DHEAS, as well as BMI. Non-PCOS obese women had higher BPA than non-PCOS non-obese women. PCOS women (both obese and non-obese) had higher BPA concentrations than non-obese controls
Ehrlich et al[24]	Prospective cohort	174	Higher BPA associated with poorer ovarian response, reduced number of mature oocytes, and reduced number of normally fertilized oocytes
Moklin et al[25]	Prospective cohort	84	Higher BPA associated with poorer ovarian response.

Continued.

Authors	Study design	Sample size	Outcome
Kandarki et al[26]	Cross sectional	171	Serum BPA was significantly higher in PCOS women and obese women (both in the control and PCOS subgroups). There was a significant positive association between BPA and androgen concentration. BPA was positively correlated with insulin resistance.
Tarantino et al[27]	Cross sectional	60	Women with PCOS had significantly higher serum BPA. BPA associated with increased spleen size. PCOS women with higher serum BPA had more severe insulin resistance
Evanthia et al[28]	Case control	71	Serum levels of BPA were significantly higher in the PCOS group than the control group. Moreover, insulin resistance and testosterone levels are also positively correlated.
Zhou et al[29]	Cross sectional	268	A mean concentration of 2.35 ng/ml was detected in the urine of women with PCOS, being a higher level than the one recorded in other women without this pathology
Rashidi et al[30]	Case control	51	Serum BPA level is significantly higher in PCOS women compared to women without PCOS. Urinary BPA levels positively correlated with BMI. urinary BPA level was statistically significant in women who had irregular menstrual cycle
Galloway et al[31]	Cross sectional	715	Urinary BPA was higher with increasing BMI/waist size. s increased SHBG with higher BPA concentrations
Wang et al[32]	Cross sectional	3390	Higher urinary BPA was significantly associated with increased BMI, abdominal obesity, and insulin resistance
Nakamura et al[33]	Methylation-sensitive quantitative PCR	6	Direct effect of BPA on DNA methylation
Trantino et al[27]	Case control	234	Positive correlation between androgen level and BPA
Fernandez et al[34]	SD rats		Altered ovarian morphology / large number of cysts
Adewale et al[35]	Long Evans rats		Disrupted ovarian development

It was noteworthy that BPA could be found in all human serum samples, and that serum BPA concentrations were substantially greater in the normal male group than in the normal female group. Notably, these BPA levels were higher than those reported to impair preimplantation development. This study is the first to use ELISA to measure serum BPA amounts in individuals and identify gender differences. We explored two possible reasons for the findings: BPA stimulating testosterone synthesis or testosterone suppressing BPA metabolism. The variance in serum BPA amounts can also be attributed to metabolic differences.[22] The study found BPA in all human serum samples, with considerably greater quantities in non-obese and obese PCOS groups compared to the normal control group. The obese normal control group had considerably higher serum BPA concentrations than the non-obese control group, indicating a positive association between BPA levels and BMI. Serum BPA concentrations were also shown to be strongly linked with serum testosterone levels in all participants. Obesity is linked to peripheral insulin resistance and hyperinsulinemia.[23] Urinary BPA levels were found to have a negative correlation with ovarian response, as measured by oocyte retrieval per cycle and peak serum E2 concentrations on HCG administration days. Serum E2 levels and oocyte yield after controlled ovarian hyperstimulation are strong indicators of successful IVF results. Although human evidence is limited, animal and in vitro studies consistently show that increasing BPA levels lead to lower ovarian E2 production.[24] Urine BPA concentrations were found to be inversely related to the number of oocytes retrieved per cycle, with an average drop of 12% for each log unit rise in SG-BPA. The number of recovered oocytes was highly linked with peak blood oestradiol concentrations. Urinary BPA concentrations showed an inverse relationship with peak serum oestradiol levels. The decrease in peak oestradiol matched their findings on recovered oocytes and supported their hypothesis that BPA negatively impacts ovarian responsiveness to controlled hyperstimulation.[25] The study found a robust link between BPA levels, HS, and low-grade inflammatory indicators in premenopausal women with PCOS, namely spleen size, highlighting the liver-spleen axis in this condition.[27] Men's serum total testosterone concentration increased in correlation with higher BPA excretion on a daily basis. Urine BPA concentrations were inversely correlated with the oestradiol: testosterone ratio and positively correlated with the FSH and FSH: inhibin ratios. since the two hormones thought to be most indicative of semen quality are FSH and inhibin B. BPA may have different effects on

the metabolism of oestrogen and testosterone. BPA was found to enhance the synthesis of testosterone and the mRNA expression of steroidogenic enzymes in a study on the production of steroid hormones in rat ovarian cells.[31]

CONCLUSION

BPA has estrogenic property and binds to oestrogen receptors α and β. Stimulation of ovarian theca cells and dysregulation of steroid biosynthesis leads to androgen overproduction. It stimulates GnRH pulse generator, decreasing the level of LH hence fertility is affected. BPA also interact with adipose tissue receptors and causes differentiation, lipid deposition and inhibition of adiponectin. Its serum and urinary levels are found to be elevated in PCOS patient. In animal studies, it is found that BPA exposure causes impaired folliculogenesis, insulin resistance and DNA methylation. EDC exposure, especially BPA which is an integral constituent of many industrial and daily use items may cause PCOS possibly by altering androgen synthesis, adipocyte stimulation and epigenetic modification there are only handful of studies conducted in Asian population and nil so far Indian population is concerned. Therefore, studies targeting Indian population are much needed.

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