Review Article

# A Systematic Review on the Relationship of Bisphenol-A with PCOS, with a Focus on Pakistan

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**ABSTRACT**

**The study was done to show the association of high bisphenol-A levels with polycystic ovarian syndrome, keeping Pakistan in focus. Google Scholar, PubMed, ScienceDirect, and DOAJ were used for the literature search. Original research articles from 2018 to 2023 were included in this review. A total of 86 articles were extracted. After exclusion, fourteen (16) articles were included in the review. No human studies were found in Pakistan, the USA, Canada, Australia, or Europe. All studies included in the review were case-control studies. Most of these studies (14) showed a positive relationship between BPA levels and PCOS, but two studies could not. No animal or human studies were found in Pakistan. Only one study was found in humans in Pakistan, which showed a direct relation between BPA levels in urine and insulin resistance in diabetic patients. According to global studies, BPA was a possible etiological factor for PCOS. No such data was obtained from Pakistan, but evidence of high levels of BPA in tap water and various canned and bottled drinks in Pakistan was found. BPA should be considered an actual threat in Pakistan at the national level. So, studies must be done, and regulations must be made to control BPA use.**

**KEYWORDS: Polycystic ovarian syndrome, PCOS, Bisphenol-A, EDCs, Pakistan**

## INTRODUCTION

Polycystic ovarian syndrome (PCOS) is the most common metabolic disorder in women of reproductive age. The estimated global prevalence of PCOS is between 5% and 15%.[1] Women with PCOS experience symptoms related to menstrual dysfunction and androgen excess. These symptoms harm the quality of life of these women. They are also at an elevated risk of comorbidities like obesity, type 2 diabetes, and thyroid disease.[2] The estimated prevalence of PCOS in Pakistan is 17.6%.[3]

Bisphenol A (BPA) is one of the endocrine-disrupting chemicals (EDCs), a group of substances that are believed to be potential contributors to the development of PCOS.[4] BPA produces many types of epoxy resins and polycarbonate plastics in baby feeding bottles, resin linings of drinks, water bottles, and food and juice cans.[5] BPA is released from these items through leaching. In 2010, WHO and the FAO recommended that BPA was a harmful substance and suggested using other materials to replace BPA, like glass and silicone.[6]

The situation is unsatisfactory in developing countries like Pakistan, where Bisphenol-A is not considered a threat. Not enough data is available regarding Bisphenol-A levels in food, making it very difficult to estimate the dietary intake of BPA in Pakistan.[7] Like other developing countries, not enough of a budget is allocated to health-related issues in Pakistan due to poverty and mismanagement at the government level.[7] In this systematic review, the population in focus was PCOS patients, exposure in focus was BPA in the serum or urine of study participants, and the outcome to be examined was a positive correlation between BPA and the occurrence of PCOS.

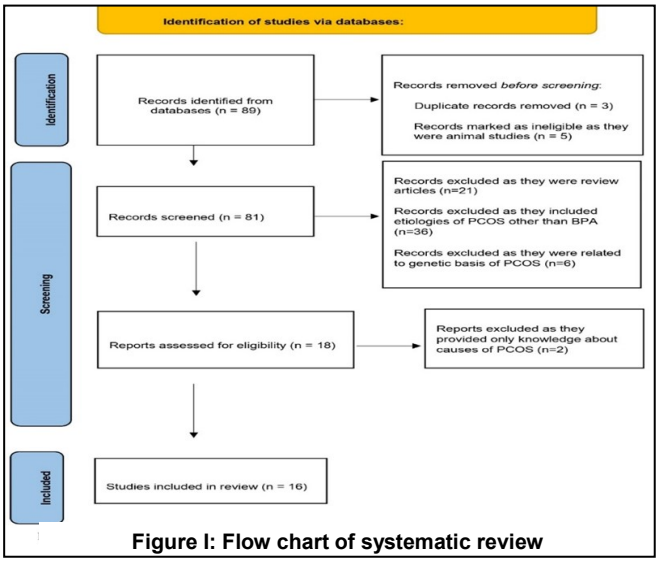


**Figure I: Flow chart of systematic review**

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*doi: 10.22442/jlumhs.2024.01100*
*Received: 09-01-2024* *Revised: 27-02-2024*
*Accepted: 16-04-2024* *Published Online: 27-06-2024*

## METHODOLOGY

Researchers were medical doctors and dietitians. This systematic review was registered with INPLASY on August 31, 2023, under the registration number INPLASY202380132, with DOI number 10.37766/ inplasy2023.8.0132. Google Scholar, PubMed, ScienceDirect, and DOAJ were used for the literature search on Microsoft 365. The search was carried out using the keywords "polycystic ovarian disease", "PCOS", "Bisphenol A", "EDCs", and "Pakistan". The original work, in English only, from 2018 to 2023, was considered in this review. Inclusion criteria were original research and human studies, including polycystic ovarian syndrome patients with high Bisphenol-A levels in serum or urine, which showed a relationship between PCOS and BPA level. Exclusion criteria were review articles, abstracts only, unpublished articles, animal studies, conditions other than PCOS cases, and EDCs other than BPA. The time taken for the synthesis of the review was three months.

A total of 89 articles were extracted. Five (05) articles were excluded from the study because they were animal studies. Three (03) articles were removed as they were duplicates of other articles included in the search. Twenty-one (21) articles were excluded because they were reviews and not original research articles. Thirty-six (36) articles were excluded because they were not related to our study objective, i.e., they were about the etiologies of PCOS other than BPA. Six (06) articles were removed because they were associated with the genetic basis of PCOS etiology. Two (02) articles were removed as they only mentioned knowledge regarding PCOS etiology. Hence, we had fourteen (14) articles to include in the review.

Interestingly, no human studies on this topic were found in Pakistan. Similarly, no human studies from the USA, Canada, Australia, or Europe could be found in the last five (05) years showing an association of BPA with PCOS. One author was contacted to get permission to use a figure from her article. Two reviewers searched and screened the literature. A Cohen's kappa score of 0.8 was obtained. Two reviewers drafted the findings, and yet another finalized and approved the manuscript. AMSTAR 2 was used to assess the quality of the systematic review. Referencing was done by using the Zotero app.

## RESULTS

Out of 16 studies extracted for the review, three studies were from Poland, two studies each were from Egypt, India, Iraq, and China, and one study each was from Iran, Turkey, Serbia, Bangladesh, Slovakia, and the Czech Republic (Table 1).[8-23] All these studies were case-control studies. No human studies in Pakistan, the USA, Canada, Australia, or Europe showed an association of Bisphenol A with PCOS. Fourteen (14) of these studies showed a positive relationship between BPA levels and PCOS, but two (02) studies could not establish any relationship. Eight (08) of these studies used urinary BPA levels, and the remaining eight (08) used serum BPA levels. In all these studies, except two, PCOS diagnosis was done according to Rotterdam criteria (ESHRE/ASRM), i.e., based on any two of the following: oligo-anovulation (OA), clinical or biochemical Hyperandrogenism (HA), and polycystic ovary morphology (PCOM) on ultrasound.[24] Following the Rotterdam criteria, four phenotypes can be determined: oligo/anovulation plus Hyperandrogenism plus polycystic ovaries, oligo/ anovulation plus Hyperandrogenism, Hyperandrogenism plus polycystic ovaries, and oligo/ anovulation plus polycystic ovaries.[25] No human studies were found in Pakistan, USA, Canada, Australia, or Europe which could show an association of Bisphenol A with PCOS.

No animal or human studies were found on the relationship between PCOS and BPA in Pakistan. Some studies in Pakistan, however, showed high levels of BPA in tap water and various canned and bottled drinks.[26,27] Only one study was found in humans in Pakistan, showing a direct relation between BPA concentration in urine and insulin resistance in diabetic patients[28]. Still, no such study was done on PCOS patients. One study was done on fish *Catla catla,* which showed that the exposure of sexually immature virgin *C. catla* to Bisphenol-A caused inhibition of FSH by increasing 17 β-estradiol concentrations.[29]

## DISCUSSION

Our review showed higher BPA levels in PCOS patients compared to controls in almost all the studies included in the review. However, two studies failed to show any relationship between these two. We could not find human studies in the USA, Europe, Canada, and Australia to establish a relationship between BPA and PCOS. However, all the studies were done on animal models in these countries. We could, however, find human studies in developing countries like India, Turkey, etc (**Table I**), but no animal or human studies were found in Pakistan. Only studies in Pakistan regarding BPA were those that showed high levels of BPA in tap water and various canned and bottled drinks.[26,27] Only one human study in Pakistan showed a positive correlation between BPA and insulin resistance in diabetic patients.[28] One animal study was done on fish *Catla* to show inhibition of FSH (by increasing 17 β-estradiol concentrations) by exposing sexually immature fish to BPA.[29] Studies in languages other than English were not included in the review because the authors believed that restricting the literature search to English had little impact on the results of the reviews.[30] The quality of studies included in our review was assessed by the tool AMSTAR 2.

**Table I: Characteristics and findings of studies included in the review**

| First author, Year | Country | Study design | Participants | PCOS diagnosis/ Body fluid used for BPA level | Findings |
|---|---|---|---|---|---|
| Zhan, 2023[8] | China | Case-control study | 321 PCOS* patients/ 412 healthy controls | Rotterdam criteria/ Urine | Environmental exposure to bisphenol A was associated with increased odds of PCOS, more in overweight and obese women. |
| Kawa, 2019[9] | India | Case-control study | 49 PCOS patients/39 healthy controls | Rotterdam criteria/ Blood serum | BPA plays an essential role in the pathogenesis of PCOS |
| Prabhu, 2023[10] | India | Case-control study | 120 PCOS patients/119 healthy controls | Rotterdam criteria/ Urine | Metabolic changes were observed in BPA-exposed PCOS women |
| Rutkowska, 2020 [11] | Poland | Case-control study | 35 PCOS patients/44 healthy controls | Rotterdam Criteria/ Blood serum | BPA* exposure may be a critical environmental factor that possibly exacerbates the disruption of hormonal balance in PCOS. |
| Akgul, 2019[12] | Turkey | Case-control study | 62 PCOS patients/ 33 healthy controls | Rotterdam Criteria / Urine | BPA could develop PCOS in adolescents. |
| Konieczna, 2018 [13] | Poland | Case-control study | 106 PCOS patients/80 healthy controls | Androgen Excess Society (2006)/ Blood serum | Serum BPA concentrations in women with PCOS are significantly higher than in age- and BMI-matched controls and also correlate positively with serum total TST and FAI (free androgen index) |
| Milanović, 2020[14] | Serbia | Case-control study | 14 PCOS BPA (+) patients/15 PCOS BPA (-) patients | Rotterdam Criteria/ Urine | BPA exposure in PCOS women caused increased obesity, insulin resistance, and elevated androgen levels. |
| Lazúrová, 2021[15] | Slovakia | Case-control study | 86 PCOS patients/32 healthy controls | Rotterdam Criteria/ Urine | PCOS women had significantly higher U-BPA concentrations than healthy controls. |
| Shaheed, 2021[16] | Iraq | Case-control study | 60 PCOS patients/30 healthy controls | Rotterdam Criteria/ Blood serum | The study showed a significant elevation in serum BPA levels in patients with PCOs compared to the control group. |
| Elkafrawy, 2021[17] | Egypt | Case-control study | 80 PCOS patients/80 healthy controls | Rotterdam Criteria/ Urine | BPA may influence the hormonal profile of infertile women (both PCOS and non-PCOS) |
| Chowdhury, 2021 [18] | Bangladesh | Case-control study | 40 PCOS patients/40 healthy controls | Rotterdam Criteria/ Blood serum | Higher BPA levels might be associated with adverse reproductive features in PCOS. |
| Jafar, 2022[19] | Iraq | Case-control study | 40 PCOS patients/40 healthy controls | Rotterdam Criteria/ Blood serum | A highly significant positive relation of Bisphenol A was found with PCOS |
| Fathy, 2022[20] | Egypt | Case-control study | 60 PCOS patients/60 healthy controls | Rotterdam Criteria/ Urine | There is a positive correlation between elevated Bisphenol-A levels and PCO. |
| Simkova, 2020[21] | Czech Republic | Case-control study | 19 PCOS patients/20 healthy controls | NIH‡ 1990 & Rotterdam criteria/ Blood serum | BPA plays a role in the PCOS |
| Gu, 2019[22] | China | Case-control study | 40 PCOS patients/83 healthy controls | Rotterdam Criteria/ Urine | Urinary BPA concentrations did not differ between the studied groups |
| Jurewicz, 2020[23] | Poland | Case-control study | 199 PCOS patients/158 healthy controls | Androgen Excess and PCOS Society (AES&PCOS) criteria /Blood serum | Serum BPA concentrations did not differ between the studied groups |

**Polycystic Ovarian syndrome, †Bisphenol-A, ‡ National Institute of Health*

***Sources of BPA:***

Bisphenol A (BPA) has been suggested as a potential xenohormone in women. It mimics estrogen action and/or antagonizes testosterone action and alters the follicle-stimulating and luteinizing hormones' secretions.[31] Bisphenol A is a universally used substance in everyday life. It can affect humans through oral, transdermal, and inhalational routes. The essential sources of Bisphenol-A include food packing material, healthcare equipment, dental materials, thermal paper, and products for youngsters. Food items are the primary source of Bisphenol-A, and the

most crucial source is canned foods. It might also be present in fresh foods like milk, meat, and eggs when water contaminates animals. BPA is used in cans for food preservation and inside coatings of jar caps. Heating the cans during food preparation or sterilization causes the BPA to leak into the canned food. Foods with high acidity and more fats also contain higher concentrations of BPA. High BPA levels may also be caused by using plastic reusable containers for food, water bottles, or bottles for youngsters, especially during heating and cooking in microwave ovens.[32, 33]

BPA in thermal paper is in monomeric form. It can result in easy transfer of BPA to the human body. This transfer is even ten times higher when the skin is wet or greasy. The penetration of BPA in the skin is very deep and cannot be washed. Cashiers handling the receipts are the most exposed to BPA.[34]

***Detection of BPA in body fluids:***

Free BPA in the blood is the most relevant measure as it interacts with the estrogen receptors. However, after oral exposure, the biological half-life of BPA in humans is less than six hours.[35] Hence, deficient concentrations are detected in the general population. Therefore, this is a disadvantage of this test. BPA entering the body via the oral route is transported to the liver after absorption. It is rapidly metabolized before reaching circulation. This metabolism step mainly produces BPA glucuronide (BPA-G). Hence, most BPA circulating in the blood following oral exposure is in conjugated forms. Only about 5% of BPA circulates freely in the blood. The BPA-conjugates are excreted in the urine. BPA-G detection is usually done in urine. BPA-G is considered a promising biomarker of exposure, although it is much less informative regarding biological effects.[35] High-pressure liquid chromatography (HPLC) is used to detect BPA in urine. Neither accepted normal serum nor urine levels of BPA were found, nor was there any accepted lowest observed adverse effect level (LOAEL) in the literature.

***Effect of BPA on ovaries:***

During a normal menstrual cycle, the recruitment of antral follicles occurs cyclically. Cohorts of the ovarian follicles grow and degenerate simultaneously till one prominent follicle, which is ≥10 mm, is chosen for growth. An increase in the follicle count and follicle-stimulating hormone (FSH) establishes the arrangement of follicles, and luteinizing hormone (LH) receptors expression in the dominant follicle and estradiol production is linked with the choice of the follicle that has to grow. Adequate estradiol production from the prominent follicle gives the required signals to cause an LH rise, ovulation, and advancement to the luteal phase. PCOS reflects disordered folliculogenesis. An increased number of follicles, from the primary stage (0.06 millimetres) to the small antral stage (2 to 5 millimetres), occurs due to the increased growth of the primordial pool of follicles, delayed maturation of these primary follicles and/or diminished loss of these follicles by atresia.[36] This concurrent scarcity of large follicles, i.e., follicles >5 millimetres, is assumed to occur due to both follicular and endocrine problems. High LH levels can increase ovarian androgen levels. Androgens then cause increased follicular growth to the recruitable stage (2 to 5 millimetres). Decreased FSH levels may inhibit further growth. Granulosa cells from polycystic ovaries (PCO) also show early response to LH in follicles that are ≤4 mm in size. These abnormalities probably abort follicular growth at the 6 to 9 millimetres phase. This termination of follicular growth is called "follicular arrest". Androgens may hinder atresia, leading to a situation where some follicles remain at the largest diameters for a longer time. This failure of follicular diminution is called "follicular persistence".[36] BPA can affect ovarian theca cells and can enhance the outpouring of androgens.[37] BPA can also attack granulosa cells. Ovarian androgens escalate as a response to FSH in PCOS, but FSH does not directly affect theca cells. Hence, BPA might directly or indirectly escalate androgen levels by affecting theca cells.[37,38] Hyperandrogenism can also lead to anovulation and polycystic ovaries. Animal studies treated with androgens showed increased follicular recruitment, leading to an increased accumulation of pre-antral and antral follicles in ovaries, leading to polycystic ovaries (**Figure II**).[38] Treatment of androgens has shown an increase in the expression of FSH and LH receptors on granulosa cells of

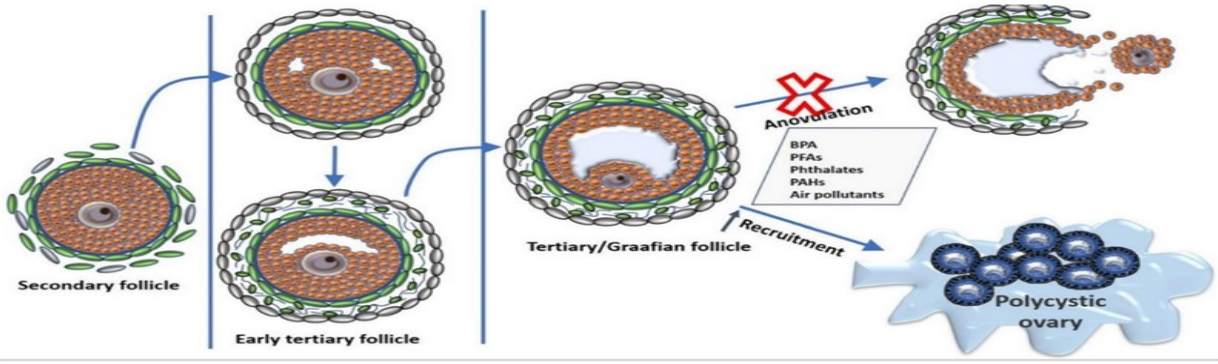


**Fig 2:** EDCs cause anovulation and recruitment of follicles causing polycystic ovaries: (Courtesy: Priya et al.[37])

anovulatory follicles. Hence, BPA seems estrogenic in its receptor binding and androgenic in its hormonal effects.[38] BPA acts on other hormonal systems related to obesity and insulin regulation. Continuously raised insulin levels are caused by BPA acting on peripheral tissues, causing insulin resistance.[37]

***History of restrictions on BPA:***

The disrupting effects of BPA on the endocrine system were first identified in 1997 in the USA.[39] After that, several studies in the USA provided proof of the disrupting effect of Bisphenol-A on body hormones. WHO and FAO mutually devised a network that expressed its uncertainty over the risks of BPA. However, in 2010, the WHO suggested restrictions on BPA, suggesting that studies have not been conclusive on adverse health effects. In 2013, the WHO reviewed Bisphenol-A toxicity. IOMC disclosed that the effects were not similar in different species. Further studies were required to assess the impact of Bisphenol-A in other animals because human testes were more sensitive than mouse testes. Generally, the WHO was uncertain about the toxicity of Bisphenol-A. In 2008, the FDA studied animal studies and established a safe level for Bisphenol-A as five mg per kg body weight per day for humans. In 2014, the FDA published a literature review on bisphenol summarising over 300 publications and declaring that BPA was okay for use in food-related plastics. USEPA is a federal agency that monitors and sets standards for environmental protection. USEPA observed the prolonged harmful effects of Bisphenol-A on the reproductive health of marine animals. Although the agency does not say anything absolute about the toxicity of BPA, it advertises that the public should decrease BPA exposure and should use BPA-free products.[39]

In 2002, the European Authority of Food Safety set a Tolerable Daily Intake of Bisphenol-A as ten micrograms per kilogram, which was increased later in 2006 to 50 µg/kg body weight. After further research, EFSA reduced the Tolerable Daily Intake level to five micrograms per kilogram body weight in 2014 and decreased it to 4 µg/kg body weight in 2015. The European Union Commission's regulation limited Bisphenol-A use in the making of feeding bottles for babies. The European Union has imposed some restraints on Bisphenol-A. However, the Food Safety Authority of Europe has not decided anything on the harmful effects of Bisphenol-A on human health.[39]

The Canadian Health Ministry suggested, in 2009, to constrain the use of Bisphenol-A in children's feeder bottles. The ministry indicated that BPA should be added to the list of toxic substances. Canada was the first country which implemented limitations on the use of BPA.[39]

Australia and New Zealand have not imposed any regulatory actions on BPA use. However, they asked for the abandonment of Bisphenol-A from use in infant milk bottles. In Australia and New Zealand, the food packed in plastics is scanned.[39]

Only a few countries utilized limiting steps on BPA use in plastics used for contact with food items. About forty countries limited the making or at least limited the use of Bisphenol-A in plastics that encounter food items.[39] The European Union, Brazil, Argentina, Turkey, and Ecuador have also limited the use of BPA. Japan and low-income countries like Pakistan, India, Bangladesh, Mexico, Egypt, Nigeria, and Indonesia have no limitations on using BPA. African and Asian countries, excluding China, do not have scientific know-how about health issues caused by BPA.[39] The situation is very unsatisfactory in developing countries like Pakistan. BPA is not considered a genuine concern at a national level in Pakistan. Insufficient data regarding levels of BPA in food makes the estimation of dietary intake difficult in Pakistan.[7] Poor socio-economic conditions result in poorly implemented health plans, corruption, and inadequate public health funding. These are the main reasons for developing countries like Pakistan's absence of regulations and governing bodies, the production and marketing of bisphenol-containing materials, and increased health risks.[40] Studies of bisphenols should be conducted at a national level in Pakistan to evaluate the health-related dangers to the Pakistani population.[28]

## CONCLUSION

According to various studies done in different parts of the world, BPA was found to be a possible etiological factor for PCOS. Although we did not get such data from Pakistan, we found evidence of high levels of BPA in tap water and various canned and bottled drinks in Pakistan. BPA is not considered an actual threat to PCOS in Pakistan at the national level.

**RECOMMENDATIONS:** Studies must be done, and regulations must be made to control BPA use in Pakistan.

**Conflict of Interest:** No conflicts of interest.

**Financial Disclosure / Grant Approval:** No funding agency was involved in this research.

**Data Sharing Statement:** The corresponding author can provide the data proving the findings of this study on request. Privacy or ethical restrictions bound us from sharing the data publicly.

## AUTHOR CONTRIBUTION

Pervez A: Concept of work, critical review, final approval
Tariq GS: Concept of work, Drafting, final approval
Ahmed F: Analysis of data, Drafting, final approval
Bushra S: Analysis of data, Critical review, final approval
Kashif S: Interpretation of data, Drafting, final approval
All authors are in agreement with accountability for all aspects of the work.

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