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ORIGINAL ARTICLE

Raised Bisphenol A has a Significant Association with Adverse Reproductive Manifestations Rather than Biochemical or Hormonal Aberrations in Women with Polycystic Ovary Syndrome

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Abstract

Background. Bisphenol A (BPA) is a widely used industrial element. Recently it is suspected that BPA may disrupt the endocrine system to influence the manifestations of polycystic ovary syndrome (PCOS).

Objective. This study aimed to assess serum BPA level and its association with manifestations of PCOS in women.

Methodology. This cross-sectional study included 40 young adults with PCOS and 38 age-matched control women [23.0 (20.0, 29.0) vs. 25.0 (21.0, 29.0), years, median (IQR), $p = 0.406$]. After a thorough clinical examination, fasting blood was collected in the follicular phase of the menstrual cycle to measure glucose, lipids, insulin, luteinizing hormone, follicle-stimulating hormone, total testosterone, sex hormone binding globulin, dehydroepiandrosterone sulfate, and BPA. Glucose was measured by glucose oxidase, lipids by glycerol phosphate dehydrogenase-peroxidase, all hormones including SHBG by chemiluminescent immunoassay and BPA by sandwiched enzyme-linked immunosorbent assay. Insulin resistance was measured using homeostasis model assessment of insulin resistance.

Result. Women with PCOS had significantly higher BPA levels (ng/mL) than the control group [27.30 (25.60, 33.40) vs. 24.0 (15.58, 28.70), median (IQR), $p = 0.001$]. Using the 75th percentile value of the control group, 15 (37.5%) women with PCOS had high BPA levels. Those with high BPA levels had a significantly higher frequency of menstrual regulation / abortion among women with PCOS [53.8% vs. 0%, $p = 0.005$]. Women with PCOS with a history of menstrual regulation / abortion [36.7 ± 4.9 vs. 28.5 ± 6.4, mean ± SD, $p = 0.004$] and subfertility [34.3 ± 6.8 vs. 28.5 ± 6.4, mean ± SD, $p = 0.031$] had higher levels of BPA than those without the histories. Serum BPA had no significant association or correlation with any androgenic and metabolic manifestations.

Conclusion. Raised BPA level may be associated with adverse reproductive features in PCOS.

Key words: polycystic ovary syndrome, Bisphenol A, endocrine disruptors, abortion

INTRODUCTION

Polycystic ovary syndrome (PCOS), one of the common female reproductive endocrinopathies, is characterized by irregular menstrual cycles, mild hyperandrogenism as well as poor metabolic features. Despite a wide range of manifestations, the prevalence of PCOS is high throughout the world.[1] However, its pathogenesis is not fully unmasked as yet. Recent studies suggest that environmental factors like Bisphenol A (BPA) may play an important role in increasing the prevalence of this syndrome by interfering with hormone-sensitive systems.[2] BPA is an endocrine-disrupting chemical found in different materials made up of plastics and epoxy resins used for food packaging, the lining of cans, cosmetics, plastic consumer products, etc.[3] It can enter our body by different routes and can produce hyperandrogenemia by various mechanisms. This includes increased ovarian synthesis and reduced catabolism of testosterone, displacing testosterone from sex-hormone binding globulin (SHBG) and up-regulating gonadotropin pulse generator activity.[4] Besides, there is a vicious relationship between BPA and androgens whereby one increases the other and vice versa. Moreover, BPA may act directly as a weak estrogen. Exposure to BPA in utero may produce early puberty, PCOS-like features, metabolic abnormalities and, later, infertility in the animal

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model.[4-6] Also, BPA may interfere with *in-vitro* fertilization.[7] However, the possible link between human exposure to BPA and manifestations of PCOS is still far from clear. This study aims to determine serum BPA levels and their associations with reproductive, androgenic and metabolic manifestations of PCOS.

METHODOLOGY

This cross-sectional study was done in the Department of Endocrinology of a University hospital for over one year. The protocol was approved by the Institutional Review Board of the same University prior to the conduct of the study. All study participants provide informed written consent. The study was conducted in accordance with the Helsinki Declaration.

The sample size was calculated using the following the formula: $n= (Z\alpha + Z_{\beta})^2 \times (\sigma_1^2 + \sigma_2^2) \div (\mu_1 - \mu_2)$.[2] Using the formula and applying the mean and standard deviation of BPA in PCOS and control from a previous study, the minimum sample size was 36.[8] In this study, we included 40 newly detected young (18-35 years) patients with PCOS and 38 age-matched control using the inclusion and exclusion criteria.

The Revised 2003 Rotterdam Consensus criteria was utilized to diagnose PCOS [presence of any two of the following: oligo/anovulation, clinical and/ or biochemical signs of hyperandrogenism and polycystic ovaries (PCO) by ultrasonography (USG); along with the exclusion of similar diseases [thyroid function abnormality (thyroid stimulating hormone: TSH <0.5 or >5.5 mIU/ml, hyperprolactinemia (>25 ng/ml), non-classic congenital adrenal hyperplasia by appropriate clinical investigations (synacthen-stimulated 17-hydroxyprogesterone >10 ng/ml)].[9] For healthy controls, regular menstrual cycle, insignificant hirsutism (modified Ferriman-Gallwey, mFG score <8) and normal free androgen index (FAI <5%) were considered as inclusion criteria. Those who had significant renal (eGFR <60 ml/ minute/1.73 m^2 body surface area) or liver disease (ALT >2 times upper limit of normal) and a history of taking any oral contraceptives, insulin-sensitizing drugs, anti-androgen, aspirin, statin, warfarin, anti-depressants, non-steroidal anti-inflammatory drugs, corticosteroid and gonadotropin-releasing hormone (GnRH) agonist/antagonist within last six months were excluded from the study.

Relevant personal and family histories (FH) were taken, and thorough physical examinations [height, weight, waist circumference (WC), blood pressure (BP), hirsutism by mFG score and acne] were done by the same investigator to maintain standardization of procedures. Fasting blood (taken 8-12 hours after the last meal) was taken from each participant during the follicular phase of the menstrual cycle (except for those with amenorrhea for whom it was done irrespective of phase) to measure luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone (TT), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S) and BPA. BPA was measured with a commercially available ELISA kit (MyBioSource Ltd., California, United States) using the double-sandwich ELISA technique. All hormones, including SHBG, were analyzed by chemiluminescent microparticle immunoassay, whereas, glucose and lipids were analyzed by glucose oxidase method and glycerol phosphate dehydrogenase-peroxidase method, respectively.

A modified mFG score of at least 8 (eight) was considered significant hirsutism, whereas a BMI of at least 25 kg/m^2 and WC of at least 80 cm were considered general and central obesity, respectively.[10,11] Free androgen index (FAI) was calculated using the following formula: (TT÷SHBG)×100% and a value ≥5 was considered as hyperandrogenemia.[12] An LH/FSH ratio (LFR) >2.0 was considered as an altered LFR.

All the data were checked for any missing or discrepant value by another senior author and corrected accordingly. SPSS Version 22.0 was used to statistically analyze the data collected. The 75th percentile value of serum BPA of the control group was used to categorize the PCOS group into high and not high BPA groups. Qualitative variables were expressed in frequencies (percentages, %). Pearson's chi-square test or Fisher's exact test (if >20% of cells had expected count <5) assessed for the association between two qualitative variables. The choice of test for association between qualitative and quantitative variables was decided considering the distribution of the quantitative variables in each subgroup of the qualitative variable. Quantitative variables were checked according to subgroups (PCOS vs. control and subgroups of different manifestations of PCOS) by the Shapiro-Wilk's test for distribution. If the quantitative variable's distribution was normal in both subgroups, a parametric test (Independent sample's t-test) was chosen (study groups vs. BMI and WC; menstrual cycle, MR/ abortion, subfertility and acanthosis nigricans category vs. BPA). Otherwise, a non-parametric test (Mann-Whitney U test) was carried out. Quantitative variables were expressed in either mean ± standard deviation (SD) or median (inter-quartile range, IQR) depending on the distributions. A Spearman's correlation test was run to assess the correlation between serum BPA (skewed distribution in PCOS) and the different variables among women with PCOS. Statistical significance was set at two-tailed p-values below 0.05.

RESULTS

Among the 40 patients with PCOS, 35 (87.5%) had irregular menstrual cycles, 34 (85.0%) had clinical and/or biochemical hyperandrogenism and 32 (80.0%) had PCO. A total of 48 participants (PCOS: 26, control: 22) were eligible for evaluation of subfertility and menstrual regulation (MR)/ abortion. Women with PCOS had a higher frequency of subfertility, family history of PCOS and obesity than the control group. They also had poor metabolic features (higher BMI, WC, systolic BP, diastolic BP, 2H-OGTT glucose, fasting insulin, HOMA-IR, TC, and LDL-cholesterol; presence of acanthosis nigricans; and lower HDL-cholesterol), greater

features of hyperandrogenism (increased presence of acne; higher levels of TT, FAI and DHEAS; and, lower SHBG) and higher LH/FSH ratio (Table 1).

Figure 1 shows that patients with PCOS had a significantly higher level of serum BPA (ng/mL) than healthy control [mean rank: 48.0 vs. 30.5, U=1101.5, p=0.001]. Using the 75th percentile value of serum BPA (28.7 ng/mL) of the control group, 15 (37.5%) women with PCOS had high BPA.

Among the different features, women with PCOS who have high BPA levels had a significantly higher frequency of only MR/ abortion than those without high BPA levels [53.8% vs. 0%, p=0.005] (Table 2).

Table 1. Characteristics of the study participants (n = 78)

Variables	PCOS, n = 40	Control, n = 38	*p*
Age, years	23.0 (20.0, 29.0)	25.0 (21.0, 29.0)	0.406*
Age of menarche, year	12.0 (11.0, 12.0)	12.0 (11.0, 13.0)	0.530*
Subfertility [n=48]	10 (38.5.0) [26]	0 (0.0) [22]	**0.001†**
Menstrual regulation/abortion [n=48]	7 (26.9) [26]	2 (9.1) [22]	0.151†
Family history of:			
Polycystic ovary syndrome	8 (20)	0 (0.0)	**0.005†**
Obesity	26 (65)	13 (32.50)	**0.004‡**
Diabetes mellitus	27 (67.5)	20 (52.6)	0.180‡
Body mass index, kg/m²	29.0±5.7	22.7±3.2	**<0.001‡**
Waist circumference, cm	92.1±13.1	77.8±9.1	**<0.001‡**
Systolic blood pressure, mm Hg	120.0 (100.0, 120.0)	110.0 (100.0, 110.0)	**0.003***
Diastolic blood pressure, mm Hg	80.0 (70.0, 85.0)	67.50 (60.0, 70.0)	**<0.001***
Acne	23 (57.5)	4 (10.5)	**<0.001‡**
Acanthosis nigricans	28 (70.0)	1 (2.6)	**<0.001‡**
LH/FSH ratio	2.0 (1.1, 2.6)	1.1 (0.7, 1.5)	**0.001***
Total testosterone, ng/dL	46.2 (30.6, 98.2)	20.7 (16.7, 26.1)	**<0.001***
Sex hormone-binding globulin, nmol/L	10.4 (8.1, 20.7)	34.1 (24.3, 64.4)	**<0.001***
Free androgen index, %	13.1 (4.7, 38.5)	1.65 (1.2, 3.2)	**<0.001***
DHEA sulfate, µgm/dL	208.6 (147.4, 301.8)	153.2 (93.8, 189.2)	**0.002***
Fasting plasma glucose, mmol/L	5.0 (4.8, 5.5)	5.20 (4.8, 5.5)	0.531*
02 hours after OGTT glucose, mmol/L	7.50 (6.2, 8.7)	6.9 (5.9, 7.2)	**0.017***
Fasting insulin, µIU/ml	11.4 (10.0, 22.7)	8.3 (6.2, 9.8)	**<0.001***
Homeostasis model assessment of IR	2.6 (2.1, 6.0)	1.8 (1.4, 2.3)	**<0.001***
Total cholesterol, mg/dL	188.5 (172.5, 210.8)	165.5 (147.5, 186.5)	**0.002***
LDL cholesterol, mg/dL	119.5 (102.3, 135.5)	99.0 (88.5, 119.8)	**0.003***
HDL cholesterol, mg/dL	46.0 (40.3, 52.5)	42.5 (37.3, 47.8)	**0.035***
Triglyceride, mg/dL	126.5 (98.0, 163.8)	105.0 (72.3, 143.5)	0.136*

Luteinizing hormone (LH), follicle-stimulating hormone (FSH), dehydroepiandrosterone (DHEA), oral glucose tolerance test (OGTT), insulin resistance (IR), low-density lipoprotein (LDL), high-density lipoprotein (HDL)

Quantitative variables were expressed in median (IQR) (skewed) or mean±SD (normal distribution) and qualitative variables in frequency (%)

Within parentheses are the percentages over the column total for qualitative variables

*Mann-Whitney U test, ‡independent samples t-test, †Fisher's exact test, and ‡Pearson's chi-square test were done, as appropriate

Table 2. Characteristics of women with PCOS according to Bisphenol A level categories (cut-off of 28.7 ng/mL) (n = 40)

Variables	High BPA, n = 15	Not high BPA, n= 25	*p*
Irregular cycle	13 (86.7)	22 (88.0)	1.000†
Subfertility [26]	7 (53.8) [13]	3 (23.1) [13]	0.107‡
Menstrual regulation/abortion [26]	7 (53.8) [13]	0 (0.0) [13]	**0.005†**
Obesity (body mass index ≥25 kg/m²)	13 (86.7)	17 (68.0)	0.269†
Central obesity (WC ≥80 cm)	14 (93.3)	20 (80.0)	0.381†
Acne	8 (53.3)	15 (60.0)	0.680‡
Acanthosis nigricans	12 (80.0)	16 (64.0)	0.477†
Significant hirsutism (mFGS ≥8)	10 (66.7)	19 (76.0)	0.716†
Hyperandrogenemia (FAI ≥5%)	11 (73.3)	19 (76.0)	1.000†
Altered LH/FSH ratio (≥2.0)	7 (46.7)	12 (48.0)	0.935‡
Insulin resistance (HOMA-IR ≥2.6)	10 (66.7)	10 (40.0)	0.102‡
Metabolic syndrome (3 out of 5 criteria)	4 (26.7)	7 (28.0)	1.000†
Polycystic ovary	11 (73.3)	21 (84.0)	0.444†

Waist circumference (WC), modified Ferriman-Gallwey score (mFGS), free androgen index (FAI), luteinizing hormone (LH), follicle-stimulating hormone (FSH), homeostasis model assessment of insulin resistance (HOMA-IR)

Within parentheses are the percentages over the column total

†Fisher's exact test and ‡Pearson's chi-square test were done as appropriate

Among women with PCOS, having a history of MR/abortion [mean rank: 20.4 vs. 11.0, U=115, p=0.004] and subfertility [mean rank: 17.6 vs. 10.9, U=121.0, p=0.031] had higher levels of BPA than those without unfavorable reproductive histories (Table 3).

Serum BPA had no significant correlation with any of the studied variables among women with PCOS (Table 4) including BMI, 2H-OGTT glucose values and HDL-cholesterol (all ϱ<±0.1, not shown in tables).

DISCUSSION

This study found a significantly higher level of BPA among women with PCOS than in healthy controls. The presence of significant BPA levels also had significant associations with MR/abortion and subfertility in women with PCOS. However, there were no significant associations of BPA with the different androgenic and metabolic manifestations of PCOS.

Table 3. Serum bisphenol A levels with different manifestations among women with PCOS (n = 40)

Variables	Subgroups	No. (%)	Serum BPA levels	*p*
Menstrual cycle	Irregular	35 (87.5)	29.4 ± 6.7	0.975‡
	Regular	5 (12.5)	29.5 ± 5.5	
Menstrual regulation/ abortion [26]	Present	7 (26.9)	36.7 ± 4.9	**0.004**‡
	Absent	19 (73.1)	28.5 ± 6.4	
Subfertility [26]	Present	10 (38.5)	34.3 ± 6.8	**0.031**‡
	Absent	16 (61.5)	28.5 ± 6.4	
Hirsutism (modified F-G score ≥8)	Significant	29 (72.5)	26.9 (25.3 – 33.5)	0.437*
	Insignificant	11 (27.5)	27.8 (25.9 – 33.7)	
Acanthosis nigricans	Present	28 (70.0)	29.8 ± 6.8	0.617*
	Absent	12 (30.0)	28.6 ± 5.9	
Acne	Present	23 (57.5)	27.4 (24.6 – 32.4)	0.386*
	Absent	17 (42.5)	27.0 (26.1 – 36.6)	
Body mass index (≥25 kg/m²)	Obesity	30 (75.0)	27.2 (25.9 – 35.1)	0.259*
	Non-obesity	10 (25.0)	27.5 (22.6 – 29.5)	
Androgen levels (free androgen index ≥5%)	Hyperandrogenemia	30 (75.0)	27.3 (25.0 (33.9)	0.612*
	Normoandrogenemia	10 (25.0)	27.3 (26.3 – 34.9)	
LH/FSH ratio (≥2.0)	Altered	19 (47.5)	26.9 (24.6 – 34.5)	0.708*
	Normal	21 (52.5)	27.7 (25.9 – 33.1)	
HOMA-IR (≥2.6)	Insulin resistance	20 (50.0)	28.7 (26.5 – 33.4)	0.547*
	Insulin sensitive	20 (50.0)	27.1 (25.0 – 33.1)	
Metabolic syndrome (3 out of 5 criteria)	Present	11 (27.5)	26.9 (26.4 – 31.5)	0.976*
	Absent	29 (72.5)	27.4 (25.3 – 34.1)	
Polycystic ovary	Present	32 (80.0)	27.0 (25.0 – 33.4)	0.396*
	Absent	8 (20.0)	29.5 (26.2 – 35.6)	

Ferriman-Gallwey (F-G), luteinizing hormone (LH), follicle-stimulating hormone (FSH), homeostasis model assessment of insulin resistance (HOMA-IR)
Quantitative data with normal and skewed distribution were expressed in mean±SD and median (IQR) respectively
*Mann-Whitney U test and ‡independent samples t-test were done, as appropriate

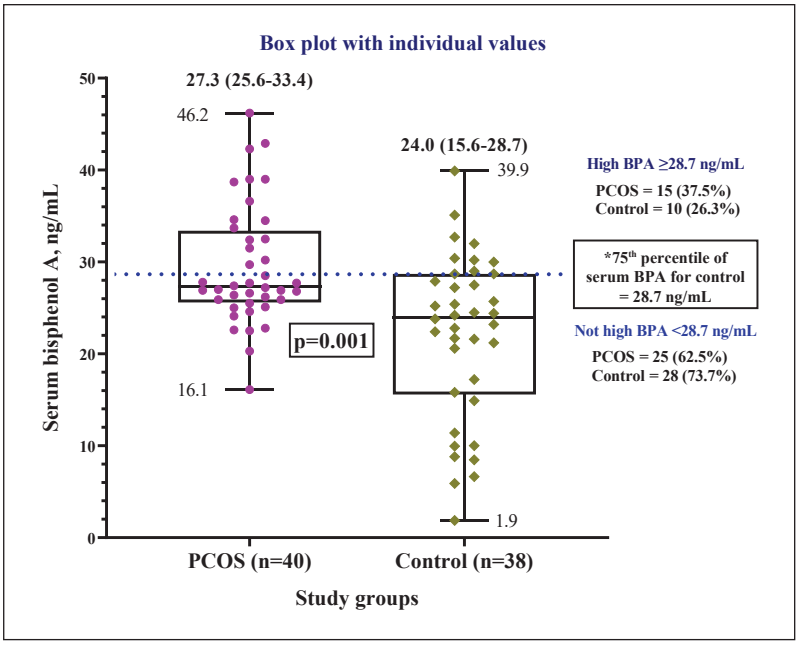

Figure 1. Serum bisphenol A levels [median (IQR)] of the PCOS group compared to the healthy control group. (n= 78)

*Based on the 75th percentile of BPA levels in the control group, study participants were divided into high (≥28.7 ng/mL) and not high (<28.7 ng/mL) BPA subgroups.

Table 4. Correlations between serum bisphenol A and different manifestations among women with PCOS (n= 40)

Variables	ρ (rho)	*p*
Age, years	0.3	0.364
Age of menarche, year	0.5	0.135
Waist circumference, cm	0.3	0.405
Systolic blood pressure, mm-Hg	-0.1	0.713
Diastolic blood pressure, mm-Hg	0.1	0.749
Modified Ferriman-Gallwey score	0.1	0.749
Total testosterone, ng/dL	0.4	0.214
Sex hormone-binding globulin, nmol/L	0.1	0.777
Free androgen index, %	0.4	0.328
DHEA sulfate, µgm/dL	-0.4	0.200
LH/FSH ratio	0.4	0.244
Fasting plasma glucose, mmol/L	-0.2	0.637
Total cholesterol, mg/dL	0.2	0.651
Low-density lipoprotein cholesterol, mg/dL	0.1	0.828
Triglyceride, mg/dL	-0.6	0.082
Fasting insulin	0.2	0.189
HOMA-IR	0.3	0.116

Luteinizing hormone (LH), follicle-stimulating hormone (FSH), dehydroepiandrosterone (DHEA), homeostasis model assessment of insulin resistance (HOMA-IR)

Spearman's correlation test was done.

We found a detectable level of BPA in all study participants. It indicates chronic exposure to BPA in the general population. It is hypothesized that the increase in the prevalence of PCOS in our setting may be attributable to industrialization and urbanization in the population and its possible interaction with unhealthy lifestyle habits. These enhance the chance of exposure to different endocrine disruptors, including BPA, which may play a role in the development of PCOS. We have seen an increased level of BPA in women of reproductive age, most of whom were from the areas around the hospital, which is located in an urban area. Moreover, control subjects also inhabit the same area as with their PCOS counterparts. The concept that incremental increases in BPA levels is associated with the presence of PCOS is unfounded. It is worth mentioning that BPA is also detectable in the control group. We can only surmise that some of them may also develop PCOS as time lapses. This is beyond the scope of this study. In the future, such studies may be done to periodically and longitudinally follow similar women to determine the link between BPA and PCOS.

Several studies also found significantly higher serum or urinary BPA in the PCOS group than in the control.[8,13-15] In this study, we observed a numerically higher BPA level in the PCOS group than in the previous studies.[8,15] A meta-analysis has shown a potential association between BPA and PCOS, as well as higher BPA in Asians than in other populations.[16] On the other hand, other authors did not find a significant difference in serum or urinary BPA levels in PCOS compared to the control group.[17,18]

Tarantino et al. (2013) found that PCOS patients with a higher level of BPA (cut-off of 0.45 ng/mL, the 95th percentile of BPA in control) had significantly higher HOMA index, FAI, and inflammatory markers than those with lower (<0.45 ng/mL) BPA.[19] We did not find a significant association of higher BPA (≥28.7 ng/mL) with any androgenic or metabolic manifestations of PCOS. However, we only found a significant association of higher BPA with MR/ abortion in PCOS patients. Furthermore, these women with a history of MR/abortion and subfertility had a higher level of serum BPA than those without. These indicate that BPA may create an adverse environment in the early development of the embryo. Studies have also shown significantly higher BPA levels in ovarian follicles and fetal amniotic fluid that may affect preimplantation development of embryos via estrogen receptors.[20,21]

We did not find significant association of BPA with any previously studied androgenic manifestations in PCOS. Our findings are consistent with Jerwickz et al. (2021).[22] While some studies found significant positive associations of BPA with androgenic features, others found a negative association.[8,13,1] Similarly, we did not find significant associations of BPA with any metabolic features of PCOS. Konieczna et al. (2018) and Akgül et al. (2019) also did not find significant associations of BPA with any metabolic manifestations in PCOS.[15,23] However, some authors have found significant associations of BPA with different metabolic manifestations in PCOS.[8,24,25] So, the exact associations of BPA with different manifestations of PCOS are not yet fully elucidated.

Although the sample size was adequate for the assessment of the association between BPA and PCOS, it was not sufficient enough to run a regression analysis to see the independent association between BPA and PCOS or its manifestations. The cross-sectional nature of the study design cannot provide a causal relationship between BPA and PCOS. Due to limitations, we could not measure serum estradiol, androstenedione and free testosterone in our study participants. Moreover, we were unable to assess the exposure level of the study participants to BPA.

CONCLUSION

In conclusion, BPA is detectable in all the study participants with a significantly higher level in the PCOS group in whom it may be associated with MR/abortion and subfertility. BPA is not associated with other reproductive, hormonal and metabolic manifestations in women with PCOS. It is hoped that the study findings will help clinicians as well as policymakers to understand the possible adverse roles of BPA in human reproduction. A larger sample size with a longitudinal study design may provide further clarification about the role of BPA in the pathogenesis of PCOS.

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Statement of Authorship
All authors certified fulfilment of ICMJE authorship criteria.

CRediT Author Statement

EURC: Conceptualization, Methodology, Formal analysis, Investigation, Data Curation, Original draft preparation, Funding acquisition; **HB**: Conceptualization, Methodology, Validation, Writing – review and editing, Supervision; **MSM:** Conceptualization, Methodology, Formal Analysis, Data Curation, Writing – original draft preparation, Visualization; **IAJ**: Conceptualization, Methodology, Investigation, Writing – original draft preparation, Visualization; **SK**: Conceptualization, Methodology, Investigation, Data Curation, Writing – Original draft preparation; **MAH**: Conceptualization, Methodology, Validation, Resources, Writing – review and editing, Supervision, Project administration, Funding acquisition.

Data Availability Statement

Datasets analyzed in the study are under license and not publicly available for sharing.

Authors Disclosure

The authors declared no conflict of interest.

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