

Endocrine Disruptors and Polycystic Ovary Syndrome (PCOS): Elevated Serum Levels of Bisphenol A in Women with PCOS

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Context: Bisphenol A (BPA) is a widespread industrial compound used in the synthesis of polycarbonate plastics. In experimental animals, neonatal exposure to BPA results in a polycystic ovary-like syndrome (PCOS) in adulthood. A bidirectional interaction between androgens and BPA levels has been disclosed.

Objective: To determine BPA levels in PCOS women as well as the association between BPA and hormonal/metabolic parameters compared to a control group.

Design, Setting, and Participants: Cross-sectional study of 71 PCOS (National Institutes of Health criteria) and 100 normal women, age- and body mass index-matched, in a University hospital setting.

Main Outcome Measures: Anthropometric, hormonal, metabolic parameters and BPA blood levels were determined. Patients (PCOS) and controls (C) were further subdivided according to body mass index into lean and overweight subgroups, respectively.

Results: BPA levels were significantly higher in the total PCOS group compared with the controls (1.05 ± 0.56 vs. 0.72 ± 0.37 ng/ml, $P < 0.001$). PCOS women, lean (PCOS-L) and overweight (PCOS-OW), had higher BPA levels compared to the corresponding control group lean (C-L) and overweight (C-OW): (PCOS-L = 1.13 ± 0.63 vs. C-L = 0.70 ± 0.36 , $P < 0.001$) (PCOS-OW = 0.96 ± 0.46 vs. C-OW = 0.72 ± 0.39 , $P < 0.05$). A significant association of testosterone ($r = 0.192$, $P < 0.05$) and androstenedione ($r = 0.257$, $P < 0.05$) with BPA was observed. Multiple regression analysis for BPA showed significant correlation with the existence of PCOS ($r = 0.497$, $P < 0.05$). BPA was also positively correlated with insulin resistance (Matsuda index) in the PCOS group ($r = 0.273$, $P < 0.05$).

Conclusions: Higher BPA levels in PCOS women compared to controls and a statistically significant positive association between androgens and BPA point to a potential role of this endocrine disruptor in PCOS pathophysiology. (*J Clin Endocrinol Metab* 96: E480–E484, 2011)

Bisphenol A (BPA), an estrogen-mimic industrial compound, is one of the world's most widely produced synthetic chemicals and is used in food and drink packaging, plastic consumer products, and dental materials (1, 2). Hu-

man exposure to BPA, one of the most abundant endocrine disruptors, is considered widespread and continuous (3–5).

The female gonad appears to be a particularly sensitive target of BPA disruption, this indicated by evidence of

interference with ovarian steroidogenesis, folliculogenesis, and ovarian morphology (6–8). The underlying mechanisms of BPA that impact upon ovarian function appear to be bidirectional. Specifically, *in vitro* studies have provided evidence that exposure of rat ovarian theca-interstitial cells to BPA results in elevated testosterone synthesis (9). Androgens interfere with BPA clearance in the liver leading to increased serum levels of BPA (10). Moreover, BPA alters androgen metabolism in the liver and, acting as a potent sex hormone-binding globulin (SHBG) binder, displaces androgens resulting in increased levels of serum free androgens (11).

Hyperandrogenaemia, insulin resistance, and chronic anovulation are the cardinal features of polycystic ovary syndrome (PCOS), the most common endocrinopathy of women of reproductive age (12). Insulin resistance is found in the majority of obese women with PCOS and in a significant proportion (30%) of lean women with the syndrome. Moreover, the prevalence of carbohydrate metabolism disorders, such as impaired glucose tolerance or frank diabetes mellitus, is significantly increased in women with PCOS compared with body mass index (BMI)-matched peers. Although the etiology of the syndrome remains enigmatic, the potential influence of environmental factors on PCOS development has recently been explored (13, 14). BPA may contribute to the pathogenesis of the syndrome, because elevated BPA levels have been reported in women with ovulatory dysfunction compared with regularly ovulating women (15). Furthermore, sex is significantly associated with BPA levels given that serum BPA concentrations are significantly higher in men than in women (16). Recently, it was shown that exposure of neonatal rats to BPA is linked with PCOS-like syndrome (17–18) and dysregulation of insulin secretion/glucose metabolism (19).

In the present study, the aim was to measure serum BPA levels in women with PCOS and to explore a possible link between BPA and hormonal/metabolic abnormalities characterizing the syndrome. A matched cohort without PCOS was used as controls. It was found that BPA levels were significantly higher in PCOS in comparison to controls, independently of BMI. Furthermore, higher levels of BPA were also related to hyperandrogenism and insulin resistance indices.

Patients and Methods

Subjects

The PCOS group comprised 71 women who were referred to the PCOS endocrine clinic due to menstrual irregularities. The enrolled population was in good health and not suffering from chronic or acute diseases. The diagnosis of PCOS was based on

National Institutes of Health (NIH) Consensus criteria (20). Chronic anovulation was assessed by less than eight cycles per year and serum progesterone levels were < 3 ng/ml during the study period. Hyperandrogenemia was assessed as total testosterone levels above the 95th percentile of the levels detected in the group of normal menstruating women. Other androgen excess disorders (congenital adrenal hyperplasia) were excluded accordingly. A Synacthen test was conducted in each woman with a basal 17-hydroxyprogesterone (17OHP) plasma level >1.0 ng/ml.

One hundred healthy women with regular periods and no hyperandrogenemia, hirsutism, or acne served as the control group, studied during the follicular phase (progesterone < 5 ng/ml). All control subjects were euthyroid, normoandrogenemic, normoprolactinemic, and none had 17OHP >1.0 ng/ml. Exclusion criteria for the study included age > 40 yr, known cardiovascular disease, neoplasms, current smoking, diabetes mellitus, renal impairment (serum creatinine >120 μ mol/liter), and hypertension (blood pressure > 140/85 mm Hg). Oral contraceptives or other drugs involved in carbohydrate metabolism, if administered, were discontinued for at least 3 months before the study.

The local ethics board approved the study protocol, and informed consent was obtained from all participants. The studied subjects were subdivided into two groups according to their BMI: the lean (defined as BMI < 25 kg/m²) subgroup and the overweight (BMI \geq 25 kg/m²) subgroup.

Assays

After 3 d of a high-carbohydrate diet (300 g/day) and an overnight fast, a standard 2-hour oral glucose tolerance test (75 g) was performed in all women. Blood sampling was conducted during the early follicular phase (d 2–4 from the first day of spontaneous bleeding episode) or at any time in anovulatory women with progesterone levels < 5 ng/ml. They were centrifuged immediately, and serum was stored at –80 C until assayed for BPA, insulin, total testosterone, SHBG, androstenedione (Δ 4A), LH, FSH, 17OHP, and dehydroepiandrosterone sulfate (DHEAS), as previously described (21). Free androgen index (FAI) was calculated by the formula: FAI = (testosterone in nmol/liter / SHBG in nmol/liter) \times 100.

The serum concentrations of BPA were measured with a commercially available ELISA kit (IBL Co., Ltd., Gunma, Japan) designed for the quantitative determination of BPA in human serum or plasma samples. The kit has a measurement range of 0.3–100 ng/ml BPA and is based on a competitive ELISA protocol using the antirabbit IgG antibody solid-phase method. All standards and samples were measured in duplicate, and all experimental procedures were carried out according to the manufacturer's instructions. The assay shows 100% cross-reactivity with BPA, 85% with BPA-Glucuronide, and 68% with BPA-Na-Sulfate. In accordance with the manufacturer's instructions, the ranges of the intra- and interassay coefficients of variation were 5.5–14.0 and 4.3–5.2%, respectively.

Insulin resistance indices

The following insulin resistance indices were calculated: 1) homeostasis model assessment for insulin resistance, calculated using the formula: fasting plasma glucose (mmol/liter) \times fasting insulin (mIU/ml)/22.5; 2) the area under the curve for glucose (AUCGLU) and insulin (AUCINS) during oral glucose tolerance

test calculated by the trapezoidal rule; 3) the insulinogenic index, calculated using the formula: $(I_{30'} - I_0') / (G_{30'} - G_0')$; 4) the ratio of insulinogenic index *vs.* homeostasis model assessment for insulin resistance, an adjusted measure of β -cell function; and 5) the Matsuda index defined as: $[10,000 / \text{square root of } (\text{fasting glucose} \times \text{fasting insulin}) \times (\text{mean glucose} \times \text{mean insulin during oral glucose tolerance test})]$.

Statistical analysis

All continuous variables showed normal distribution, as was documented by the use of the Kolmogorov–Smirnov test. Data are presented as means and SD. The two-tailed unpaired *t* test was used to evaluate the differences in normally distributed variables between the two groups and Bonferroni's correction for *post hoc* comparisons. The Pearson correlation coefficient was applied to assess the correlation between the variables. Multiple regression analysis was used to examine the relationship of BPA with the characteristic components of PCOS. All tests are two-sided, and statistical significance was set at $P < 0.05$. All analyses were carried out using the statistical package SPSS version 13.00 (SPSS Inc., Chicago, IL).

Results

Serum BPA concentrations were significantly higher in the PCOS group compared with controls (1.05 ± 0.56 *vs.* 0.72 ± 0.37 ng/ml, $P < 0.0001$). Serum levels of testosterone, DHEAS, $\Delta 4$, 17OHP, LH/FSH ratio, and FAI were significantly higher in the entire PCOS group compared with the controls, while serum levels of SHBG were significantly lower. Additionally, the PCOS group showed lower insulin sensitivity as defined by a statistically significant lower Matsuda index ($P < 0.05$) and higher AUC-GLU and AUC-INS ($P < 0.05$ and $P < 0.0001$, respectively) compared with controls (Table 1).

Both PCOS and controls (C) were divided in two subgroups according to their BMI, which were designated as lean (L) ($\text{BMI} < 25 \text{ kg/m}^2$) and overweight (OW)

($\text{BMI} \geq 25 \text{ kg/m}^2$). PCOS-L as well as PCOS-OW were comparable for age and BMI with their corresponding control groups (C-L and C-OW), respectively. In lean women with PCOS, BPA values were significantly higher compared with lean controls (1.13 ± 0.63 *vs.* 0.70 ± 0.36 ng/ml, $P < 0.001$) and the same difference was observed in the obese subgroups (0.96 ± 0.46 ng/ml, 0.72 ± 0.39 , $P < 0.05$) (Fig. 1). Both lean and obese women with PCOS had significantly higher androgens and LH/FSH ratio, while SHBG levels were lower compared with those in the respective subgroups of controls ($P < 0.001$). In both PCOS subgroups, the AUC-INS was significantly increased compared with the respective control groups, and in obese PCOS women the Matsuda index was lower than obese controls ($P < 0.05$). Pertinent data are analytically depicted in Table 1.

From Pearson analysis in the total group (PCOS and C), a significant positive correlation of BPA with testosterone ($r = 0.192$, $P < 0.05$) and androstenedione ($r = 0.257$, $P < 0.05$) was noted. Moreover, in the PCOS group a positive correlation between BPA and Matsuda index was observed ($r = 0.273$, $P < 0.05$). When multiple regression analysis was carried out in the total group using BPA as the dependent variable, a significant correlation with the existence of PCOS was found ($r = 0.497$, $P < 0.05$).

Discussion

These data clearly show that serum BPA levels are significantly higher in women with PCOS in comparison to their normal ovulating nonhyperandrogenemic peers, independently of the degree of obesity. Multiple regression analysis disclosed a strong association of BPA with PCOS existence and, additionally, Pearson analysis unraveled a significant association between BPA and androgens levels.

TABLE 1. Results in the total group, as well as in lean and obese subgroups

	PCOS (n = 71)	Controls (n = 100)	Lean PCOS (n = 38)	Lean controls (n = 51)	Obese PCOS (n = 33)	Obese controls (n = 49)
Age, yr	28.45 \pm 4.80	32.43 \pm 5.35	29.32 \pm 5.71	31.33 \pm 6.22	27.15 \pm 2.10	33.13 \pm 3.25
BMI, kg/m ²	27.36 \pm 7.74	27.2402 \pm 8.43	21.37 \pm 1.90	21.46 \pm 1.67	34.55 \pm 5.66	34.16 \pm 8.05
BPA, ng/ml	1.05 \pm 0.56***	0.72 \pm 0.37	1.13 \pm 0.63	0.70 \pm 0.36**	0.96 \pm 0.46	0.72 \pm 0.39*
Testosterone, ng/dl	102.56 \pm 34.50***	35.56 \pm 13.67	99.25 \pm 37.30	35.84 \pm 13.57***	106.75 \pm 31.50	34.4 \pm 13.77***
SHBG, nmol/liter	36.69 \pm 16.94***	72.68 \pm 47.13	45.40 \pm 13.58	84.74 \pm 48.28***	27.64 \pm 14.53	59.89 \pm 42.47***
FAI	13.07 \pm 1.05*	8.84 \pm 0.89	16.14 \pm 8.33	10.77 \pm 7.91*	9.01 \pm 1.39	6.61 \pm 1.09
DHEAS, ng/ml	2242 \pm 458***	1970 \pm 992	2369 \pm 1294	1885 \pm 762	2029 \pm 940	2024 \pm 844
$\Delta 4$, ng/ml	3.71 \pm 1.24***	1.80 \pm 0.47	3.70 \pm 1.31	1.79 \pm 0.46***	3.80 \pm 1.13	1.82 \pm 0.49***
17OHP, ng/ml	1.53 \pm 0.75***	0.79 \pm 0.36	1.63 \pm .815	0.76 \pm 0.31***	1.34 \pm 0.59	0.83 \pm 0.42***
LH/FSH	1.33 \pm 0.85***	0.78 \pm 0.36	1.41 \pm .92	0.82 \pm 0.37**	1.22 \pm 0.77	0.74 \pm 0.35**
HOMA-IR	2.84 \pm 0.27	2.28 \pm 0.24	2.21 \pm 0.35	1.68 \pm 0.12	3.66 \pm 0.39	3.03 \pm 0.49
INSINDEX	1.40 \pm 0.30	1.05 \pm 0.98	0.88 \pm 0.34	0.33 \pm 0.46	1.93 \pm 0.50	2.25 \pm 0.93
AUC-GLU	13,550 \pm 3,035***	14,892 \pm 3,365	12,533 \pm 3,130	13,774 \pm 2,439	14,709 \pm 2,519	16,154 \pm 3,899
AUC-INS	8,279 \pm 4,220***	5,373 \pm 2,051	7,169 \pm 3,675	5,250 \pm 2,446*	9,526 \pm 4,625	5,580 \pm 3,851*
MATSUDA INDEX	5.76 \pm 0.49***	7.25 \pm 0.55	7.26 \pm 0.76	7.66 \pm 0.85	3.98 \pm 2.42	6.6 \pm 3.88*
INS.INDEX/HOMA	0.63 \pm 0.17	0.91 \pm 0.75	0.44 \pm 0.24	0.25 \pm 0.89	0.81 \pm 0.27	2.00 \pm 1.11

*, $P < 0.05$; **, $P < 0.001$; ***, $P < 0.0001$, between PCOS and controls.

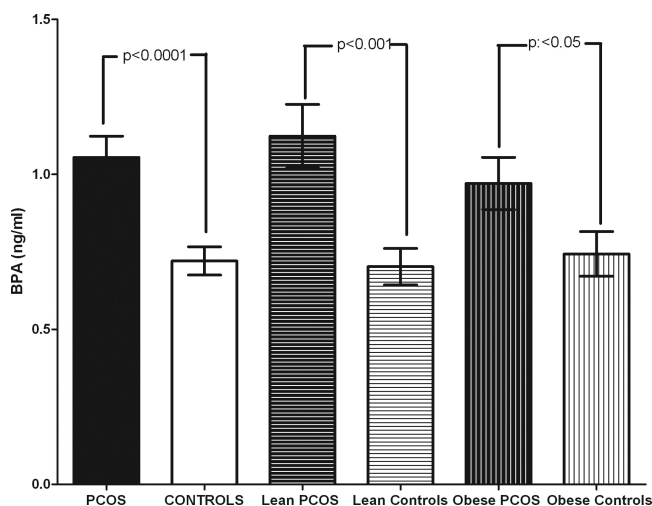


FIG. 1. BPA values in PCOS and controls, as well as in lean and obese subgroups.

PCOS, characterized by chronic anovulation and hyperandrogenism according to NIH criteria constitutes the most common endocrine disorder of women of reproductive age (20). Although the pathogenesis of the syndrome has not as yet been fully unraveled, the role of environmental factors has been proposed as being implicated in PCOS development (22). BPA is a widespread environmental pollutant, and recent data from experimental animals have demonstrated that neonatal exposure to BPA leads to PCOS development (18). Nevertheless, human data are lacking regarding any link between this endocrine disruptor and the syndrome of polycystic ovaries.

Apart from its well-known estrogen-mimetic properties, BPA also seems to have a role in androgen metabolism. There are several lines of evidence indicating the existence of a bidirectional interaction between BPA and androgens. Specifically, it has been reported that uridine diphosphate-glucuronosyl transferase activity, a liver enzyme involved in BPA clearance from the circulation, is down-regulated by androgens (10). Additionally, BPA is a potent SHBG ligand and, accordingly, in increased concentrations, displaces androgens from SHBG binding sites and likely leads to increased circulating free androgen concentrations (23, 24). Moreover, on the other hand, it has been reported that BPA significantly inhibited the activity of two different testosterone hydroxylases (2- and 6-hydroxylase), leading to decreased testosterone catabolism and indirectly to increased testosterone concentrations (11).

Another very interesting point connecting BPA with PCOS is the observation that BPA *per se* may stimulate hyperandrogenemia in the ovary, because *in vitro* culture of rat ovarian theca-interstitial cells with BPA resulted in elevated testosterone synthesis (9). The mechanisms appear to be linked with increased mRNA expression of key

enzymes involved in steroid production pathway, including 17- α hydroxylase, cholesterol side chain cleavage enzyme, and steroidogenic acute regulatory protein (9). Interestingly, PCOS ovarian hyperandrogenism is partly attributed to activation of this steroidogenic pathway (25). Therefore, it could be suggested that increased BPA levels, as found in the PCOS population of this study, interact with the ovary carrying an inherent enzymatic defect, this leading to further enhancement of ovarian androgen production and therefore hyperandrogenemia. The connection of androgens with BPA is further supported by the positive correlation of BPA with androgens disclosed in the present study, a finding in agreement with previous reports in a small number of anovulatory women (15).

The role of insulin resistance and hyperinsulinemia in the pathogenesis of PCOS has been deduced from animal and human data (26). In the present study, a significant difference of hyperinsulinemia in PCOS women in comparison to controls, in both groups, as well as in lean and obese subgroups was observed. In addition, the degree of insulin resistance was statistically different between these groups and a positive correlation of BPA with the Matsuda index was displayed in PCOS women. Taking all these observations into account, one may speculate a possible impact of BPA in insulin action. This hypothesis is further corroborated by recent animal data showing that environmentally relevant doses of BPA have been linked to disturbance of pancreatic physiology and glucose metabolism, thus enhancing the risk for the development of insulin resistance in intact animals (19, 27).

Furthermore, the finding via multiple regression analysis that BPA is strongly associated with the existence of PCOS may imply an involvement of this chemical in PCOS pathophysiological mechanisms. Certainly, due to study design, the presented data do not detect causality in the pathophysiological mechanism linking BPA with PCOS. However, experimental data of neonatal exposure to BPA and the subsequent development of PCOS in animals are suggestive of a possible interaction of this abundant chemical compound with the hormonal and metabolic abnormalities observed in women with PCOS (6, 18).

In conclusion, in the present study it has been demonstrated that in women with PCOS, BPA levels are higher compared with BMI-matched healthy women and are positively and strongly associated with hormonal and metabolic abnormalities characterizing the syndrome. These new observations imply a potential role of this endocrine disruptor in PCOS pathophysiology. However, further investigation is required to elucidate the mechanisms linking BPA with PCOS and the possible clinical implications of these findings.

Acknowledgments

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