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Urinary concentration of personal care products and polycystic ovary syndrome: A case-control study

Jiayuan Gu[a], Tao Yuan[a,*], Ni Ni[a], Yuning Ma[a], Zhemin Shen[a], Xiaodan Yu[b], Rong Shi[c], Ying Tian[c], Wei Zhou[d], Jun Zhang[d]

[a] School of Environmental Science and Engineering, Shanghai Jiao Tong University, Shanghai 200240, China
[b] Department of Developmental and Behavioral Pediatrics, Shanghai Children's Medical Center , Shanghai Jiao Tong University, Shanghai 200127,China
[c] Department of Environmental Health, School of Public Health, Shanghai Jiao Tong University, Shanghai 200025, China
[d] Ministry of Education-Shanghai Key Laboratory of Children's Environmental Health, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200092, China

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ABSTRACT

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorder among females of reproductive age. Many emerging contaminants in personal care products have been confirmed with endocrine disruptive effects. We performed a case-control study to explore the association between the concentrations of certain emerging contaminants (organic UV filters, bisphenol A, and triclosan) and the risk of PCOS. Urine samples were collected from 40 women with PCOS (case group) and 83 healthy women (control group). No significant differences were found in detection rate or total concentrations of analytes in women with PCOS and controls ($p > 0.05$). In addition, no association was found between certain emerging contaminants and PCOS either in an unadjusted binary logistic regression model or in a model adjusted for potential confounders. However, with stratification according to body mass index, one organic UV filter - octocrylene(OC) was significantly associated with PCOS in women with BMI ≥ 24 (adjusted OR = 1.512, 95% CI: 1.043, 2.191). It's the first time to investigate the association between exposure of organic UV filters and PCOS risk. We conclude that there is positive association between OC and PCOS risk in obese and overweight women.

1. Introduction

Polycystic ovary syndrome (PCOS) is a complex heterogeneous disorder of unclear etiology characterized by chronic oligoovulation or anovulation and hyperandrogenism together with polycystic ovarian morphology (Palioura and Diamanti-Kandarakis, 2015; Wang et al., 2017). PCOS is the most common endocrine disorder among females of reproductive age, occurring in approximately 5–10% (Benrick et al., 2017; Chapman et al., 2009). The condition is associated with obesity and insulin resistance (Pasquali et al., 2011), leading to the development of type 2 diabetes (Talbott et al., 2007) and may increase the risk of breast cancer (Kim et al., 2016) and cardiovascular disease (Legro, 2009).

Although the pathogenesis of PCOS remains under investigation, both genetic and environmental factors likely contribute (Diamanti-Kandarakis et al., 2006). The endocrine disruptive effects of some personal care products (PCPs) have been of concern in recent years. PCPs contain many chemicals used for body care and appearance improvement. Bisphenol-A (BPA), triclosan (TCS), and ultraviolet filters (UVFs), such as homomethyl salicylate (HMS), benzophenone-3 (BP-3), and octocrylene (OC), are common components of PCPs. These chemicals are being frequently detected in aquatic systems (Brown et al., 2012; Montes-Grajales et al., 2017; Nasseri et al., 2017; Ramos et al., 2015, 2016), sediment (Chen et al., 2014; Guo et al., 2016; Tsui et al., 2015), marine species (Park et al., 2017; S et al., 2017) and human beings (Krause et al., 2017; Zhang et al., 2013), as consumption and bioaccumulation increase. More recently, we confirmed in our previous study that the indoor dust could be the sink of these PCPs, which indicating the individual exposure risk from daily life (Ao et al., 2017).

Exposure to PCPs during development has been hypothesized to interfere with hormone activity and the risk of endocrine disorders. For example, BPA, an organic compound used in making plastic and epoxy resins, is well-known as an estrogen-mimicking endocrine disruptor. A cross-sectional study found serum BPA level was significantly higher in

* Correspondence to: School of Environmental Science and Engineering, Shanghai Jiao Tong University, No. 800 Dongchuan Road, Minhang District, 200240 Shanghai, China.
E-mail address: taoyuan@sjtu.edu.cn (T. Yuan).

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women with PCOS compared to controls, implying a potential role of BPA in the pathophysiology of PCOS (Kandaraki et al., 2011). However, another study found BPA hardly induced any PCOS-related hallmarks in a rat model (Patisaul et al., 2014). TCS is a major antimicrobial agent in household products, cleaning supplies, and pesticides (Lenz et al., 2017), and is persistent in the environment and poorly degraded (Guo et al., 2016). Animal assays have revealed that TCS could induce concentration-dependent reduction in worm reproduction (Lenz et al., 2017) and reduce fecundity in the copepod *Trissolcus japonicus* (Park et al., 2017). Although several studies in rats failed to show that TCS possessed estrogenic activity or suppressed male reproductive function in vivo, evidence presented herein suggested that TCS could bind with low affinity to estrogen and androgen receptors and evoke weak endocrine disruptive effects (Witorsch, 2014). UVFs, especially organic UFVs, are diverse lipophilic chemicals capable of absorbing either UVA (400–320 nm) or UVB (320–280 nm) radiation and are extensively used in sunscreens, creams and other PCPs for skin protection (S et al., 2017; Witorsch and Thomas, 2010). As an emerging class of endocrine disruptors, UVFs may serve as estrogen receptor (ER) ligands and, because of their aromatic structure, induce transactivation (Durrer et al., 2005; Schreurs et al., 2005). Several studies in animals have shown that UVFs can trigger estrogenic, antiestrogenic, and/or antiandrogenic activity by regulating the expression of target genes (Christen et al., 2011; Coronado et al., 2008; Szwarcfarb et al., 2008; Zhang et al., 2017). *In vitro* study also demonstrated multiple hormonal activities of UVFs (Jimenez-Diaz et al., 2013; Kunz and Fent, 2006b; Schlumpf et al., 2004). In addition, we just reported that UVFs can induce the excretion of inflammatory cytokines in human macrophages (Ao et al., 2018). This finding suggests UVFs might play a role in PCOS development, as it was associated with inflammatory disorders (Pasquali et al., 2011; Solano et al., 2011).

Although recent investigations have focused on the bio/cytotoxicity, reproductive dysfunction and environmental impact of PCPs, research on the possible association between exposure to PCPs and PCOS is limited. The proposed link between PCPs and PCOS is based mainly on animal studies and in vitro studies, in which certain compounds are implicated. But the reliable evidence is lacking. Therefore , the aim of the present case-control study was to explore a possible association between the selected common PCP ingredients and the risk of PCOS by measuring urinary PCPs (BPA, TCS, HMS, BP-3, and OC) levels in women with and without PCOS.

2. Methods

2.1. Study design and population

Our study utilized resources from the National Basic Research Program of China (973 Program), a project comprising 2178 women from Shandong, Zhejiang province and Shanghai focusing on the impacts of environmental endocrine disruptors on female reproductive function, in which 397 were diagnosed with PCOS. Due to the territory distance and quantity of urine sample provided by eligible women, this retrospective case-control study included 123 women with no history of pregnancy, ranging from 20 to 41 years of age. Those who had other endocrine diseases or whose mother had endocrine or metabolic disorder were excluded in order to reduce confounders, since both gene and environment factor contribute to PCOS (Diamanti-Kandarakis et al., 2006). Basic information was collected through clinic interviews about education, occupation, lifestyle, medication history, etc. All participants agreed to sign the written informed consent, and all research activities were approved by the Medical Ethics Committee of Xinhua Hospital, Shanghai Jiao Tong University School of Medicine.

The case subjects consisted of 40 women who were diagnosed with PCOS according to the Rotterdam criteria (Chang et al., 2004), which required the presence of at least two of the following clinical or laboratory abnormalities: 1) oligo-ovulation or anovulation; 2) elevated levels of circulating androgens or their clinical manifestations; and 3) polycystic ovaries, as defined by ultrasonography. Eighty-three healthy women with regular menstrual cycles and no endocrine disorders were recruited as control subjects. Baseline examinations and urine sampling of eligible subjects were conducted by a local 3 A hospital (Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200092, China).

2.2. Laboratory analysis

Urine samples were stored at − 20 °C and thawed at 4 °C until the assays. The determinations of BPA, TCS, HMS, BP-3 and OC followed by our previous report for these analytes with slight modification for urine samples pretreatment (Ao et al., 2017). Briefly, with regards to conjugation of phenols and glucuronic acid, the samples of 2 ml were incubated with 1 ml β-glucuronidase at 37 °C for 12 h. After centrifugation at 8000 rpm for 10 min, the supernatant of samples was diluted to 20 ml with Milli-Q water (adjusted to pH 3 with HCl by a PHS-3C pH meter (Zhiguang Instrument and Meter Co., Ltd., Shanghai, China)) and then treated with a solid-phase extraction method using Auto SPE-06D/03D (Reeko Instrument Co., Ltd., USA) with Oasis HLB cartridges (6 ml, 200 mg; Waters Inc., Milford, MA, USA). The extract was spiked with internal standards, i.e., BP-d10 and BPA-d16 (25 μg/L) and then reconstituted by ethyl acetate to a final volume of 0.5 ml. Before injection, the solutions were derivatized for 30 min reaction using BSTFA-TMCS under room temperature. The concentrations of chemicals were subsequently measured with GC-MS/MS using a TSQ Quantum XLS gas chromatograph (RTX-5 column, 30 m 0.25 mm, 0.25 mm) and tandem mass spectrometer (Thermo Scientific) equipped with an electron ionization source (Ao et al., 2017). The limit of detection (LOD) was set at a signal-to-noise ratio (S/N) of 3 times of the average baseline. It ranged from 2.0 fg/ml to 0.5 pg/ml for the respective analytes. Recovery rates were also satisfactory which ranged from 79.5% to 98.8%, respectively. Details of methodology validation results are listed in Table S1.

All standards and samples were measured in duplicate, and all experimental procedures were carried out according to the manufacturers' instructions. Urinary creatinine concentrations were determined by an enzymatic method using an automatic biochemical analyzer (7100, Hitachi Inc., Tokyo, Japan) at Xinhua Hospital and used to adjust for interferences of variable urine dilutions. The creatinine concentrations of all selected samples were between 0.3 g/L and 3.0 g/L.

2.3. Covariates

PCOS is a heterogenous disorder with unclear etiology. Information on age at enrollment, education level, alcohol consumption, smoking history and PCPs-related lifestyle and occupation which might be relevant to the outcomes were obtained by questionnaire at the clinic interview. BMI was calculated by formula with measured height and weight. Due to all participators had no history of smoking and few of them had frequent consumption on alcohol, alcohol consumption and smoking history were excluded from confounders. In addition, the PCPs-related lifestyle was almost based on the recall and estimation of the participators. Thus, age at enrollment, education level, occupation and BMI were chosen as covariates in the adjusted models.

2.4. Statistics analysis

Descriptive variables are presented as means and SD; categorical variables are presented as frequencies with percentages; and target concentrations presented as medians (interquartile range). Any value below LOD was set as zero. The Kolmogorov-Smirnov analysis was performed for determination of normality. Spearman's rank correlation coefficient analysis was performed for determination of association between PCPs within the same sample. To compare the characteristics between case and control subjects, parametric data were analyzed with

Table 1
Demographic factors, reproductive history, and lifestyle of eligible subjects.

	case (n = 40)[a] n (%) or mean (SD)	control (n = 83)[a] n (%) or mean (SD)	p^b
Age (y)	30.5 (3.6)	29.8 (3.2)	0.297
≤ 29	16 (40.0)	44 (53.0)	0.185
≥30	24 (60.0)	39 (47.0)	
Age at menarche	14.0 (1.6)	13.8 (1.3)	0.377
LH/FSH	1.55 (0.68)	0.79 (0.30)	0.000
BMI (kg/m^2)[c]	25.0 (4.1)	23.0 (3.7)	0.007
< 18.5	2 (5.0)	7 (8.4)	
18.5–23.9	13 (32.5)	49 (59.0)	
24–27.9	14 (35.0)	20 (24.1)	
≥ 28	11 (27.5)	7 (8.4)	
Education			0.549
primary or lower	4 (10.0)	4 (4.8)	
junior high	17 (42.5)	38 (45.8)	
high school or above	19 (47.5)	41 (49.5)	
Occupational exposure to PCPs			0.172
yes	6 (25.0)	6 (11.1)	
no	18 (75.0)	48 (88.9)	
Alcohol consumption			1.000
yes	2 (5.0)	6 (7.2)	
no	38 (95.0)	77 (92.8)	
Frequency of using plastic cup			0.303
never	26 (65.0)	59 (71.9)	
sometimes	6 (15.0)	15 (18.3)	
often	3 (7.5)	5 (6.1)	
daily	5 (12.5)	3 (3.7)	
Frequency of using plastic tableware			0.438
never	27 (69.2)	66 (69.5)	
sometimes	11 (28.2)	15 (18.5)	
often	1 (2.6)	2 (2.4)	
Frequency of using sunscreen			0.422
never	8 (36.4)	16 (35.5)	
hardly	7 (31.8)	8 (17.8)	
sometimes	7 (31.8)	17(37.8)	
often	0 (0.0)	4 (8.9)	

[a] Data are mean (SD) or frequency (percentage). Total number may not be equal to the number of cases or controls because of missing or unknown data.
[b] Pearson's χ^2 test for nonparametric data or *t*-test for parametric data.
[c] BMI is classified as lean, normal, overweight or obese according to Criteria Weight for Adults (AQSIQ, 2013).

Student's *t*-test or ANOVA. The Mann-Whitney *U* test was used for analysis of nonparametric continuous data, and Chi-square test for categorical variables. Binary unconditional logistic regression was applied to estimate odds ratios (ORs) for PCOS and their corresponding 95% confidence intervals (CI). Regression model was analyzed based on the tertile distribution of PCPs concentration in control groups, and the lowest tertile was assigned as reference group.

All statistical analyses were performed with SPSS 24.0 statistical software (SPSS Inc., Chicago, IL, USA). A 2-tailed *p*-value of < 0.05 was considered significant.

3. Results and discussion

3.1. Characteristics of the study population

Characteristics of the case and control populations are given in Table 1. No statistically significant differences were seen in current age or age at menarche between women with PCOS and those without PCOS. Women with PCOS had significantly higher body mass index (BMI) and luteinizing hormone/follicle-stimulating hormone (LH/FSH) values than did control subjects ($p < 0.05$, $p < 0.001$). Abdominal obesity and LH hypersecretion are characteristic features of PCOS (Diamanti-Kandarakis et al., 2012). Although the risk of PCOS is only minimally increased with obesity (Yildiz et al., 2008), obesity is considered as an imbalanced state that exceeds the capacity to expand subcutaneous adipose, which may drive PCOS development (Virtue and Vidal-Puig, 2008). The significantly higher percentages of overweight and obese women with PCOS may reflect a phenotypic preference for PCOS.

The characteristics of subject's lifestyle were recorded through clinic interviews. Some data were unavailable in terms of consent. Nonetheless, control and case subjects appeared to be similar in education level ($p = 0.549$); in frequency of using plastic cups, plastic tableware or sunscreen ($p > 0.05$); or in frequency of using materials containing PCPs (Table S2). There was no significant difference as well in occupational exposure (yes or no) to PCPs ($p = 0.172$), while the proportion of women who chose “yes” was two-fold more in cases than in controls (25.0% vs. 11.1%). Neither group had a history of tobacco smoking. And there was no significant difference in numbers who consumed alcohol ($p > 0.05$). Thus, tobacco smoking and alcohol consumption were excluded as confounders, which was a different finding from that in an analogous study (Wang et al., 2014).

3.2. The detection rates and urine concentrations of PCPs

The detection rates and urinary concentrations of BPA, TCS, BP-3, HMS, and OC are presented in Table 2. Because the concentrations were not normally distributed, the median with interquartile range were used to describe. The unadjusted value above limit of detection (LOD) in subjects ranged from 0.01 to 161 μg/L for BPA, 0.15–53.6 μg/L for TCS, 0.57–450 μg/L for BP-3, 0.04–8.21 μg/L for HMS and

Table 2
Urinary concentrations and detection rate of BPA, TCS, BP-3, HMS, and OC.

	Detection Rate n (%)	unadjusted (μg/L) median (IQR)	creatinine adjusted (μg/g Cr) median (IQR)	p^a	p^b
BPA	Σ49 (39.8)				
case	13 (32.5)	< LOD (< LOD, 0.52)	< LOD (< LOD, 0.61)	0.326	0.201
control	36 (43.4)	< LOD (< LOD, 1.37)	< LOD (< LOD, 1.54)		
TCS	Σ29 (23.6)				
case	8 (20.0)	< LOD (< LOD, < LOD)	< LOD (< LOD, < LOD)	0.651	0.473
control	21 (25.3)	< LOD (< LOD, 0.22)	< LOD (< LOD, 0.10)		
BP − 3	Σ75 (61.0)				
case	21 (52.5)	0.77 (< LOD, 53.44)	0.59 (< LOD, 42.09)	0.237	0.447
control	54 (65.1)	8.96 (< LOD, 27.08)	14.16 (< LOD, 51.26)		
HMS	Σ34 (27.6)				
case	10 (25.0)	< LOD (< LOD, 0.06)	< LOD (< LOD, 0.07)	0.830	0.584
control	24 (28.9)	< LOD (< LOD, 0.21)	< LOD (< LOD, 0.45))		
OC	Σ87 (70.7)				
case	26 (65.0)	1.06 (< LOD, 5.72)	1.58 (< LOD, 6.30)	0.399	0.442
control	61 (73.5)	1.57 (< LOD, 4.53)	2.51 (< LOD, 6.91)		

[a] Chi-square test comparing the detection rate between cases and controls.
[b] Mann-Whitney *U* test comparing the concentration between cases and controls.

0.09–42.8 μg/L for OC, respectively. It was noted that the 2003–2004 National Health and Nutrition Examination Survey (NHANES), conducted on 2517 persons in the United States, found urinary BPA concentrations ranging from 0.4 to 149 μg/L (Calafat et al., 2008b), TCS from 2.4 to 3790 μg/L (Calafat et al., 2008c), and BP-3 from 0.4 to 21700 μg/L (Calafat et al., 2008a), which differed by race/ethnicity, age, sex, and household income. Considering the relatively small samples in our subjects and the wide range of values, it is hard to achieve the conclusive comparison with the NHANES-reported concentrations (Table S6).

In previous studies, the detection rates of BPA and TCS in urine were respectively reported as 99.8% and 92.7% in Korean adults (Kim et al., 2011), 100% and 37% in Swedish mothers (Larsson et al., 2014), and 69.2% and 99.4% in Canadian pregnant women (Arbuckle et al., 2015). The corresponding values in this study were 39.8% and 23.6%, respectively. Similar occurrence rate of BPA (38.6%) in urine was found in a Novi Sad study collecting 145 samples from women (Milic et al., 2015). Since food is the main source of BPA exposure (Huang et al., 2017), and skin penetration of cleaning products is a source of TCS (Larsson et al., 2014), it is reasonable that the detection rate of these PCPs varies among districts and individuals. On the other hand, we found that BP-3, HMS and OC were present in 61.0%, 27.6% and 70.7% of subjects' urine samples, respectively. This detection rate for BP-3 corresponds well with the range of urinary BP-3 detection rates in previous studies (25% (Zhang et al., 2013) and 80% (Frederiksen et al., 2017)). In addition, the most frequently detected analytes were OC and BP-3, which was consistent with our previous study about their detection rates in indoor dust (Ao et al., 2017).

It was noted from Table 2, neither the detection rate nor the concentrations of the five PCPs studied were significantly different between case and control subjects ($p > 0.05$).

3.3. Correlation between PCPs

Correlations between each two analytes among BPA, TCS, BP-3, HMS and OC were analyzed by Spearman's correlation test. The results are presented in Table 3. Except for BPA and TCS ($p = 0.121$), the pairs were significantly positively correlated. Given the ubiquitous presence of BPA and TCS in the environment, it is difficult to distinguish the sources of BPA and TCS intake. BP-3, HMS and OC are prevalently used, together or alone, as UVFs (Gilbert et al., 2013; Ramos et al., 2016). BPA and TCS were added into sunscreens at times for specific properties (Lu et al., 2018). The significant correlation implies homologous sources of several analytes and suggests that more emphasis should be placed on the potential synergistic effect of BPA, TCS, BP-3, HMS and OC. Moreover, the Kruskal-Wallis H test, comparing the concentrations of five chemicals among different lifestyles, incriminated the use of sunscreen in BP-3 exposure (Table S4, $p = 0.048$). Certain UVFs can enter the vascular system through penetration, permeation and resorption (Klimová et al., 2013) and are then excreted in urine. BP-3 has typically been implicated in absorption across the skin (Benson; Fernandez et al., 2001).

Table 3
Spearman rank-order correlation coefficients between PCPs.

	BPA	TCS	BP-3	HMS	OC
BPA	1.000	0.140 ($p = 0.121$)	0.358** ($p < 0.001$)	0.247** ($p = 0.006$)	0.287** ($p = 0.001$)
TCS		1.000	0.363** ($p < 0.001$)	0.323** ($p < 0.001$)	0.330** ($p < 0.001$)
BP-3			1.000	0.542** ($p < 0.001$)	0.581** ($p < 0.001$)
HMS				1.000	0.416** ($p < 0.001$)
OC					1.000

** Correlation is significant at the $p < 0.01$ level (2-tailed).

Table 4
Risk of PCOS and urinary BPA, TCS, BP-3, HMS and OC levels, stratified by BMI.

	BMI < 24.0		BMI ≥ 24	
	OR (95% CI)[b]	p	OR (95% CI)[b]	p
BPA[a]	1.013 (0.970, 1.058)	0.566	0.820 (0.491, 1.371)	0.450
TCS[a]	0.918 (0.727, 1.158)	0.469	0.113 (0.001, 17.989)	0.399
BP-3[a]	1.001 (0.997, 1.005)	0.631	0.994 (0.964, 1.025)	0.718
HMS[a]	1.428 (0.737, 2.766)	0.291	1.143 (0.187, 6.984)	0.885
OC[a]	0.848 (0.699, 1.030)	0.096	1.512 (1.043, 2.191)	0.029

[a] Creatinine adjusted concentration level. (μg/g Cr).
[b] Adjusted odds ratio for current age, educational level and occupational exposure.

The Mann-Whitney *U* test (Table S4) found that TCS levels were significantly higher in women employed in the pharmacy or chemical engineering industries than in those not in these occupations ($p = 0.043$). This observation supports the opinions that PCPs are the main source of TCSs (Hong et al., 2014) and that exposure in daily life explain, in part, the differences in urinary concentrations.

3.4. Association between PCPs and PCOS

The associations between PCOS and BPA, TCS, BP-3, HMS and OC exposure are summarized in Table S5. PCOS is a heterogenous disorder with different phenotypes, for which obesity is a common feature but not a primary role (Diamanti-Kandarakis et al., 2012). Given that a significant difference of BMI was observed between study subjects, eligible women were categorized into subgroups based on BMI according to Chinese criteria weight for adults (AQSIQ, 2013) to alleviate confounding. Table 4 presents the risk of PCOS with creatinine-adjusted urinary BPA, TCS, BP-3, HMS and OC levels in subgroups. There was no association between BPA, TCS, BP-3 and HMS concentrations and PCOS according to the adjusted logistic regression models. However, a statistically significant association between OC and PCOS was observed ($p = 0.029$) when BMI was ≥ 24, which is the level of overweight in China [Adjusted OR = 1.512 (95% CI: 1.043, 2.191)]. Thus, our result suggests that OC exposure is an environmental pathogenic factor for PCOS among overweight and obese women.

To further explore the possible dose-response effect of OC exposure, Table 5 presents the overall crude and adjusted ORs and 95% CIs, additionally adjusted ORs and *p* for trend in subgroups for PCOS according to the tertiles of creatinine-adjusted OC concentrations in urine, respectively. No significant positive trend was found between PCOS risk and increasing levels of OC in the all analysis model (p trend > 0.05). Nevertheless, in the adjusted model OR for the medium tertile was 7.348 (95% CI: 0.324–166.8) and for the highest tertile was 15.236 (95% CI: 1.053–220.4), compared to the lowest tertile when BMI ≥ 24.

To our knowledge, this is the first case-control study to report the association between PCOS and UVFs. Published data have documented interference of BPA with reproductive and metabolic activity (Rochester, 2013). Exposure to BPA could contribute to weight problems in women (Milic et al., 2015), and higher BPA levels in follicular fluid were found in women with PCOS (Tsutsumi, 2005). BPA may alter developmental pathways and cell processes and lead to changes in the estrogen-target organs, such as ovary and uterus, through binding with different receptors (Rezg et al., 2014), but a significant relationship between BPA and PCOS has not been found to date. Similarly, there is little evidence that TCS exposure through PCPs use presents a risk of endocrine-disruptive adverse health effects in humans (Witorsch, 2014). While TCS is similar to BPA and 17β-estradiol in chemical structures (Wang and Tian, 2015), associations between either BPA or TCS exposure and PCOS was not observed in this study.

On the other hand, hormonal activity of UVFs has been

Table 5
Risk of PCOS associated with urinary OC levels, stratified by BMI.

OC[b]	n	Unadjusted		adjusted		BMI < 24[a]		BMI ≥ 24[a]	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
T1	41	1.000 (ref)		1.000 (ref)		1.000 (ref)		1.000 (ref)	
T2	41	0.713 (0.280,1.816)	0.478	2.247 (0.561,8.993)	0.253	6.756 (0.571,80.003)	0.130	7.348 (0.324,166.828)	0.211
T3	41	0.837 (0.303,2315)	0.732	2.613 (0.596, 11.458)	0.203	2.898 (0.162,50.765)	0.469	15.236 (1.053, 220.449)	0.046
p_{trend}			0.777		0.398		0.281		0.133

[a] Adjusted odds ratio for current age, educational level and occupational exposure.
[b] OC levels (μg/g creatinine): T1 (≤0.46), T2 (0.46–4.40), T3 (> 4.40).

demonstrated in rats (Klammer et al., 2005), invertebrates (Ozaez et al., 2013, 2014) and fishes (Coronado et al., 2008; Kaiser et al., 2012; Kunz et al., 2006). It has been reported that BP-3, HMS, 3-BC and 4-MBC have the estrogenic effects of antagonism toward the androgen receptor and progesterone receptor (Schreurs et al., 2005). However, Kunz and Fent found that HMS, OC and some other UVFs exhibited submaximal to full androgenic activity, especially for HMS which produced full dose–response curves in the hAR assay (Kunz and Fent, 2006b). Although there were conflicting in vitro results about estrogenic or androgenic activities of UVFs, they could play a role in reproductive dysfunction. It was reported that exposure to benzophenone-type UVFs may diminish couples' fecundity (Buck Louis et al., 2014) and may be associated with endometriosis (Kunisue et al., 2012). Additionally, UVFs could generate reactive oxygen species and might cause allergy reaction (Gilbert et al., 2013; Hanson et al., 2006). In our another study, we just confirmed the UVFs can induce the excretion of inflammatory cytokines in human macrophages (Ao et al., 2018). This new finding indicates that UVFs exposure might deteriorate PCOS development in terms of inflammatory disorders. In this study, we found no association between PCOS and BP-3 or HMS either when BMI ≥ 24 or < 24. However, OC showed a significant association with PCOS in overweight and obese women (OR = 1.512, 95%CI: 1.043, 2.191). In the previous studies, OC presented bioaccumulation effects and posed impacts to transcription of genes related to metabolic processes in the livers (Bluthgen et al., 2014), as well as accelerated ovary development at a high concentration in the zebra fish model (Zhang et al., 2016). These animal studies support the assumption that OC plays a role in etiology of PCOS through alteration on steroidogenesis and estrogenic activity. Some other researchers have found that even though individual UV filter was present at a no-observed-effect concentration, the UV filter mixtures might cause substantial combined effects (Kunz and Fent, 2006a). And the metabolites of certain UVFs retain or even reinforce estrogenic activity (Watanabe et al., 2015). Furthermore, time effect and gene susceptibility are also influential factors of PCOS development (Yuan et al., 2015). Thus, additional researches on combined effect of PCPs in vivo and in vitro are needed to understand the underlying mechanisms. Also, the relevant longitudinal study in larger population is needed to clarify the association between PCPs and risk of PCOS.

4. Conclusion

We found urinary OC concentrations and PCOS were positively associated in women with BMI ≥ 24, whereas no dose-dependent effect was observed. There were no significant relationships between PCOS and urinary BPA, TCS, BP-3, HMS, and OC levels, respectively, in overall case-control group. In addition, our discussions such as the paradoxical mechanism and mixtures exposure effects of certain PCPs, stir up the concern of their roles on the development of PCOS.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.envres.2018.09.014.

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