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

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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

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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