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Association of serum organochlorine pesticides concentrations with reproductive hormone levels and polycystic ovary syndrome in a Chinese population

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HIGHLIGHTS

- PCOS is caused by a combination of genetic susceptibility and environmental exposures.
- Patients with PCOS had higher *p,p′*-DDT (P = 0.016) and *o,p′*-DDT levels than the controls.
- *o,p′*-DDT may play a role in the pathogenesis of PCOS related with reproductive hormone levels.

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ABSTRACT

To investigate the serum concentrations of organochlorine pesticides (OCPs) in patients with polycystic ovary syndrome (PCOS), a total of 178 women were studied. The concentrations of hexachlorocyclohexane (HCH) and dichlorodiphenyltrichloroethane (DDT) in serum were determined using Gas Chromatography Mass-Mass Spectrometer. No differences with statistical significance in the mean HCH, *p,p′*-DDD, *p,p′*-DDE concentrations were observed between the patients with PCOS and the control group. Serum *p,p′*-DDT (P = 0.016) and *o,p′*-DDT (P = 0.000) levels were significantly higher in patients with PCOS compared with the control group. The results of the association between OCPs levels and hormone levels indicated that *o,p′*-DDT may play a role in the pathogenesis of PCOS by affecting hormones levels. Further trials should be investigated with the findings in this study to obtain new pathogenesis of PCOS.

1. Introduction

Polycystic ovary syndrome (PCOS) is a highly prevalent heterogeneous syndrome of clinical and/or biochemical androgen excess, ovulatory dysfunction and polycystic ovaries (Goodarzi et al., 2011). PCOS is the most common cause of anovulatory

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; DCM, dichloromethane; DDD, dichlorodiphenyldichloroethane; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; DHEAS, dehydroepiandrosterone-sulfate; E2, estradiol; EDCs, exogenous endocrine disrupting chemicals; FSH, follicle-stimulating hormone; GC-MS-MS, chromatography mass-mass spectrometer; GIR, fasting glucose/insulin ratio; HCH, hexachlorocyclohexane; HDL-C, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment; IR, insulin resistance; LDL-C, low-density lipoprotein cholesterol; LH, luteinizing hormone; LOD, limit of detection; OCPs, organochlorine pesticides; PCOS, polycystic ovary syndrome; PLS-DA, partial least-squares-discriminant analysis; POPs, persistent organic pollutants; PRL, progesterone; QUICKI, quantitative insulin sensitivity check index; SBP, systolic blood pressure; SHBG, sex hormone binding globulin; T2DM, type 2 diabetes mellitus; TSH, thyroid-stimulating hormone; WHR, waist-to-hip ratio; YLDs, lived with disability.

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infertility among all known causes of infertility (Teede et al., 2010). Two-thirds of women with PCOS have metabolic dysfunction and have an increased risk of developing type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). PCOS is also associated with obesity, insulin resistance (IR) and endometrial carcinoma (Lin et al., 2012). PCOS affects 5–10% of reproductive-aged women worldwide, with prevalence among the Han Chinese population of 5.6% (Li et al., 2013).

The pathogenesis of PCOS has not been fully elucidated. However, the results of many studies demonstrated that PCOS is caused by a multifactorial etiology of genetic susceptibility and environmental exposures. A preliminary family studies have suggested the familial aggregation of hyperandrogenemia in PCOS kindreds (Legro et al., 1998). On the other hand, several preliminary studies show that environmental pollutants are involved in severe reproductive and endocrine disorders (Craig et al., 2011; Johansson et al., 2016; Yang et al., 2015).

Persistent organic pollutants (POPs) are ubiquitous contaminants that are not readily degraded in the environment and can accumulate in biota, including humans. Most of these contaminants are endocrine-disrupting chemicals (EDCs) and may interfere with the synthesis, secretion, transport and metabolism of endogenous hormones (Yang et al., 2015). Prenatal exposure to mixtures of human relevant EDCs can have negative consequences on the female reproductive system later in life (Johansson et al., 2016).

Organochlorine pesticides (OCPs) including dichlorodiphenyltrichloroethane (DDT) and hexachlorobenzene (HCH) are ubiquitous in the environment following many years of agriculture use. DDT is one of the most well known OCPs. It was applied worldwide as an insecticide for vector control until the 1970s, and is still used in some countries (van den Berg, 2009). A recent study shows that six OCPs including DDT and HCH are found in 8.2% nut samples of China, with the concentrations of 2.0 μg kg^{-1} to 65.7 μg kg^{-1} (Liu et al., 2016). In the environment and in living organisms, DDT is mainly degraded to *p,p′*-dichlorodiphenyldichloroethylene (*p,p′*-DDE), which is even more persistent than the parent compound. In China, DDT is still produced for export for malaria control and for domestic use in dicofol production. Unlike technical DDT, dicofol use in China is mainly in the southern and eastern provinces, especially in Fujian, mostly on litchi, longan, and citrus crops. DDT pollution in Fujian is very likely dominated by dicofol type DDT pollution, which means that the concentrations of *o,p′*-DDT are higher than normal area (Qiu et al., 2005; Zheng et al., 2016).

Prenatal exposure to OCPs in Southern Spain has an impact on the weight of healthy full-term newborns (Monteagudo et al., 2016). DDT has been found to interact with androgen receptors and estrogen receptors (Li et al., 2008; Soto et al., 1995). DDT induces adverse effects on male rat fertility by acting directly on the testes and altering the neuroendocrine function (Patrick et al., 2016; Rhouma et al., 2001). There are several evidences suggesting that OCPs might be involved in reproductive hormone levels and thereby possibly also in the development of PCOS. A study used Partial least-squares-discriminant analysis (PLS-DA) confirm that serum concentrations of *p,p′*-DDE are associated with PCOS (Yang et al., 2015). However, studies on DDT pollution in China have paid little attention to *o,p′*-DDT, and few research show the serum *o,p′*-DDT levels in relation to PCOS. Keeping in view the dicofol type DDT pollution in Fujian, the serum OCPs concentrations associated with PCOS and hormone concentrations was investigated in the present study. Our objective in this study was to identify the relationship between serum concentrations of OCPs and hormones and to assess the possible impact of exposure to OCPs on PCOS.

2. Materials and methods

2.1. Study subjects and data collection

Blood serum samples were recruited from women at the Reproductive Medicine Center of 174th Hospital of PLA (Xiamen, China) between 1 March 2013 and 31 August 2013, and stored at −80 °C. All of women were from Xiamen and its surrounding cities and this area is not an industrial area. Among these samples, 84 women were PCOS patients. The patients of PCOS was defined when at least two of the following three features were present: oligo-/amenorrhea (<8 menstrual cycles in the presenting year); hyperandrogenism (and/or hirsutism); and polycystic ovaries (Rotterdam EA-SPcwg, 2004). In order to carry out control, we randomly selected 94 samples. None of the controls had symptoms of hyperandrogenism, a history of menstrual dysfunction, infertility, or sonographic signs of PCOS. All subjects were non-pregnant, non-smokers. All women were studied within the first 10 days after onset of menstruation in the case of mild oligomenorrhea or at random in those suffering from severe oligo- or amenorrhea. The characteristics of PCOS women and controls were summarized in Table 1, and their concentrations were determined following the published methods (Zheng et al., 2015).

2.2. Ethical approval

The present study was approved by the Reproductive Medicine Center of 174th Hospital of PLA (Xiamen, China), and informed consent was obtained from all participants prior to their recruitment into the study.

2.3. Analysis of OCPs

The methods were based on previous study with some modifications (Hagmar et al., 2006). Before extraction, the surrogates ^{13}C-β-HCH, ^{13}C-*p,p′*-DDT(20 ng) were spiked separately into the serum. Samples are kept at 4 °C overnight for equilibrium before sample extraction. The HLB column (500 mg, Waters, USA) was washed with dichloromethane (DCM) and activated with methanol and Milli-Q water. After conditioning, 1 mL serum was added into column with moist column. The column was then dried for 30 min by aspiration of ambient air. Subsequently, 18 mL of DCM: *n*-hexane (1:1, v/v) was added to the column for elution. Dried sodium sulfate column was used for the cleaning of extract. After extraction, the solvents were evaporated down to 0.5 mL under a gentle stream of nitrogen gas, and then, 20 ng of internal standard PCB-103 was added before analysis by Gas Chromatography Mass-Mass Spectrometer (GC-MSMS).

OCPs were determined with a Trace 1310 gas chromatograph (GC) coupled with TSQ 8000 mass selective detector (MSD) and a 50 m × 0.25 mm DB-5 capillary column (Agilent, USA). The GC injector temperature was 290 °C with splitless mode, and the GC oven temperature was programmed as follows: 80 °C for 2 min, increased 20 °C/min to 200 °C, held for 2 min, increased to 250 °C at a rate of 2 °C/min, followed by a rate of 25 °C/min to 300 °C, and then held for 15 min.

2.4. Quality assurance/Quality control

A solvent blank and a procedural blank were added for every sequence of 10 samples to ensure that the samples and the analysis process were free of contamination. The retention times matched with those of the authentic reference compounds and the signal to noise (S/N) ratio was greater than three for the selected ions. The