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Endocrine-Disrupting Chemicals: Possible Genesis of Ovarian Tumors

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Abstract

Background: Prolonged exposure to environmental toxicants like endocrine-disrupting chemicals has been linked to several ovarian pathologies. Exposure to endocrine-disrupting chemicals may start at any time of life from the fetal stage to adulthood resulting in various health complications The purpose of our study is to compare the concentration levels and association of benzopyrene, bisphenol A and genistein in patients with ovarian tumors and normal control group. We also sort to evaluate the predictive performance of benzopyrene, bisphenol A and genistein in patients with ovarian tumors. **Methods:** A case-control study was conducted for randomly selected participants involving 30 patients and 30 controls. 30 patients with radiologically diagnosed and histopathological confirmed ovarian tumors were included in the study between January 2022 and December 2022. Urine samples from each group were analyzed using liquid chromatography-mass spectrometry. Descriptive analysis for normally distributed continuous variables was done accordingly. Concentration levels of endocrine-disrupting chemicals were assessed using the Mann-Whitney test. The association of endocrine-disrupting chemicals with pathological ovarian tumors was analyzed using binary logistic regression. Evaluation of the diagnostic performance of endocrine-disrupting chemicals was analyzed using the ROC curve. **Results:** Overall, patients were significantly (P = 0.000) older than the healthy controls. Mean years (SD) were 36.7 (7.90) and 28.8 years (4.89) for patients and normal women respectively. Endometriomas had the highest incidence of 50%. The level of benzopyrene and bisphenol A in patients was significantly higher than those in the control group, while the level of genistein was significantly higher in normal controls. Benzopyrene and bisphenol A were significantly associated with ovarian cysts, and the incidence of pathological ovarian cysts was positively correlated to these EDCs,

with OR value 64.79 (P = 0.005) for benzopyrene and 9.609 (P = 0.001) for bisphenol A. Genistein was significantly negatively correlated with the incidence of pathological ovarian tumors, with OR value of 0.153 (P = 0.007). Diagnostic performance on the AUC for benzopyrene, bisphenol A and genistein reached 0.765 (P = 0.0004), 0.769 (P = 0.0003) and 0.649 respectively. **Conclusion:** Benzopyrene and bisphenol A might be potential novel predictive molecular biomarkers or be involved in the pathogenesis of pathological ovarian cysts while genistein may have preventive or inhibitory effects.

Keywords

Environmental Toxicants, Endocrine-Disrupting Chemical, Ovarian Cyst, Ovarian Tumor

1. Introduction

The actual prevalence of ovarian tumors is unknown, as many patients are believed to have no symptoms and are undiagnosed, but many researchers have reported an incidence of 8% - 18% [1]. Ovarian cysts are divided into 2 main categories, namely physiological and pathological [2]. Physiological ovarian cysts occur as a result of the normal menstrual cycle while the pathological cyst isn't related to the menstrual cycle. Pathological ovarian cysts are considered as ovarian tumors, which can be benign, malignant and borderline. Benign tumors are more common in young females, but malignant ones are more frequent in elderly women [3].

Some of the risk factors for ovarian cysts include infertility treatment [4], drugs like tamoxifen [5], pregnancy [6], maternal gonadotropins [7], cigarette smoking [8] and tubal ligation [9]. In recent times, the environmental pollution caused by urbanization and industrialization has been reported to affect human health globally [10] [11]. These environmental toxicants are chemical compounds in our environment due to various processes, including manufacturing, combustion, leaching from products, and human contamination [12]. Most of the environmental toxicants are known endocrine-disrupting chemicals (EDCs) [13]. EDCs are chemicals or chemical mixtures, which interfere with normal hormone action [14]. This is of concern because women are exposed to EDCs on a daily basis, some EDCs are known to target the ovary and cause reproductive health problems, such as endometriosis, infertility, premature ovarian failure and abnormal sex steroid hormone levels. Exposure to EDCs may occur by ingestion of water, food and dust, via inhalation of gases and air particles and via dermal absorption of cosmetics and/or substances deriving from thermal paper. Breastfeeding and vertical transmission of EDCs have been demonstrated [15] [16].

The purpose of our study is to compare the concentration levels of EDCs, namely benzo(a)pyrene, bisphenol A and genistein flavone between patients with ovarian tumors and the normal control group. We also sort to evaluate the predic-

tive performance and association of benzo(a)pyrene, bisphenol A and genistein with ovarian tumors.

2. Methodology

2.1. Participants

Randomly selected participants involving 60 participants were involved 30 patients and 30 normal control cases. Ovarian tumor patients who underwent surgery between January 2022 and December 2022 at the Second Affiliated Hospital of Nanjing Medical University were enrolled in the present study. No patients were pregnant, critically ill, on contraceptives 6 months prior to this study or had preoperative chemotherapy, radiotherapy or other treatment history or other inflammatory diseases. The 30 enrolled patients were 18 years and above. All patients had a pelvic ultrasound done for radiological diagnosis of ovarian cyst. The 30 control subjects were healthy volunteers with no current or previous history of ovarian disease.

2.2. Eligibility Criteria for Patients

2.2.1. Inclusion Criteria

- ≥18 years of age;
- Admitted female;
- Patient willing to participate;
- Ovarian tumor of any size identified by pelvic ultrasound examination;
- Ovarian tumor biopsy confirmed by histopathology.

2.2.2. Exclusion Criteria

- Patients < 18 years of age;
- Pregnant women;
- Critically ill patients;
- Contraceptive therapy within last 6 months prior to presentation;
- Comorbidities including diabetes mellitus, hypertension, renal dysfunction, polycystic ovarian syndrome, primary ovarian insufficiency or ovarian cysts
- History of chemotherapy or radiotherapy;
- Preoperative chemotherapy or radiotherapy.

2.3. Eligibility Criteria for Healthy Controls

2.3.1. Inclusion Criteria

- ≥18 years of age;
- Individuals willing to participate in the study;
- Female individuals;
- Healthy women coming for routine medical checkups or employees of the hospitals.

2.3.2. Exclusion Criteria

- Patients < 18 years of age;

- Pregnant women;
- Critically ill patients;
- Contraceptive therapy within last 6 months prior to presentation;
- Comorbidities including diabetes mellitus, hypertension, renal dysfunction, polycystic ovarian syndrome, primary ovarian insufficiency or ovarian cysts;
- History of chemotherapy or radiotherapy;
- Preoperative chemotherapy or radiotherapy.

2.4. Tissue Samples

The ovarian tissue samples were collected at the time of the curative surgery. Specimens were routinely processed for histopathological assessment to confirm the diagnosis of pathological ovarian cyst.

2.5. Urine Samples

10 ml morning mid-stream urine was collected from each participant and stored at room temperature before laboratory analysis. The samples were pretreated according to the LC/MS/MS common toxin analysis method package. Urine samples (2 ml) was first filtered with a 0.22 μm filter membrane, then added acetic acid-sodium acetate buffer (0.5 M) to adjust the pH value to 5.4, then added β-glucuronidase/arylsulfatase (10 μl) and vitamin C (5 mg), incubate overnight at room temperature to complete the enzymatic hydrolysis reaction. The samples after enzymatic digestion were subjected to solid phase extraction with SPE cartridges (C18 ENVI, 0.25 g). The extract was eluted with methanol (2 ml), dried with nitrogen, and finally redissolved with methanol (100 μl) as the analyte to be tested. 50 μl of the analyte to be tested was transferred to a liquid chromatography vial with a micro syringe for sample analysis. Before analysis of the sample, analytical conditions had to be met:

1) Liquid phase conditions: Mobile phase: Phase A: (0.1% formic acid + 5 mM ammonium formate) water, Phase B: Acetonitrile, Flow rate: 0.4 mL/min. Column temperature: 40˚C, Chromatographic column: ACQUITY UPLC BEH C18 (1.7 μm, 2.1 × 100 mm), Injection volume: 5 μl and Elution method: Gradient elution, the initial gradient ratio is 30% (Phase B).

2) Mass Spectrometry Conditions: Ion source: ESI, DL temperature: 250˚C Heating module temperature: 400˚C, Interface temperature: 300˚C, Nebulizing gas flow rate: 2.0 L/min, Drying gas flow rate: 10.0 L/min, Heater tassel: 10.0 L/min, Collision gas: Argon, Scanning mode: MRM.

3) Characteristic MRM mass spectrum: Analysis of urine was done using the analytical instrument: Shimadzu LCMS-8050CL triple quadrupole liquid mass spectrometry system (registered medical device number: 20182400195) LC-30A system, including LC-30AD × 2 (infusion pump), SIL-30AC (autosampler), CTO-30A (column thermostat), FCV-32AH (high-pressure flow switching valve) CBM-20A (system controller), DGU-20A5 (online degasser) and LabSolutions Ver. 5.60 (chromatographic workstation).

2.6. Statistical Analysis

Statistical analysis was performed using SPSS software version 23 and visualization was done by graph pad prism. Descriptive analysis for frequencies and percentages on continuous variables was done. Independent sample t test was done to compare the means for the two groups. To assess the concentration levels of EDCs we used the Mann-Whitney test analysis. Association of EDCs with pathological ovarian tumors was analyzed using binary logistic regression. Evaluation of the diagnostic performance of EDCs was analyzed using the ROC curve. Confidence interval was set at 95% and $P < 0.05$ (2-tailed) was considered statistically significant.

3. Results

3.1. Participants Demographic Characteristics

A total of 60 individuals participated in this study of which 30 had pathological ovarian cyst and the other 30 were normal health women. Overall, majority of the patients were older, and above 40 years old; more overweight, alcohol intake, parity and cigarrete smoking were seen in patients than in normal controls (Table 1).

Table 1. Demographic characteristics of patients and normal controls.

Variable	Overall N = 60	Patients N = 30 n (%)	Controls N = 30 n (%)	P-value
Age group (years), mean (SD)		**36.7 (7.90)**	**28.8 (4.89)**	
18 - 30	32 (53.3)	8 (26.7)	24 (80.0)	
31 - 40	13 (21.7)	9 (30.0)	4 (13.3)	0.000
>40	15 (25.0)	13 (43.3)	2 (6.7)	
Parity, mean (SD)		**0.87 (0.68)**	**0.67 (0.71)**	
0	23 (38.3)	9 (30.0)	14 (46.7)	
1	28 (46.7)	16 (53.3)	12 (40.0)	
2	8 (53.3)	4 (13.3)	4 (13.3)	0.271
>2	1 (1.7)	1 (3.3)	0 (0.0)	
BMI group (kg/m^2), mean (SD)		**22.7 (2.9)**	**22.4 (2.6)**	
<18.5 (underweight)	1 (1.7)	1 (3.3)	0 (0.0)	
18.5 - 24.9 (normal)	48 (80.0)	22 (73.3)	26 (86.7)	
25 - 29.9 (overweight)	11 (18.3)	7 (23.3)	4 (13.3)	0.654
≥30-obese	0 (0.0)	0 (0.0)	0 (0.0)	
Marital status,				
Married	41 (68.3)	29 (96.7)	12 (40.0)	NA
Single	19 (31.7)	1 (3.3)	18 (60.0)	
Alcohol intake				
Occasionally	6 (10.0)	5 (16.7)	1 (3.3)	NA
Never	54 (90.0)	25 (83.3)	29 (96.7)	
Cigarette smoking				
Occasionally	2 (3.3)	2 (6.7)	0 (0.0)	NA
Never	58 (96.7)	28 (93.3)	30 (100)	

3.2. Histopathology of Tissue Samples

Histopathological data of the 30 patients were analyzed (Table 2). Majority of pathological ovarian tumors were Endometriomas (15/30 cases, 50%) with lowest cases being cystadenomas (2/30 cases, 6.7%).

Table 2. Histopathological findings of the cases.

Cyst type	n (%)
Teratomas	13 (43.3)
Endometriomas	15 (50.0)
Cystadenomas	2 (6.7)
Total	**30 (100)**

3.3. Urine Concentration of Endocrine-Disrupting Chemicals (EDCs)

The results of Mann-Whitney test analysis show that the levels of benzopyrene and bisphenol A in patients with ovarian cysts are significantly higher than those in the control group, but the level of genistein is significantly lower than those in the control group (P = 0.001) (Figure 1).

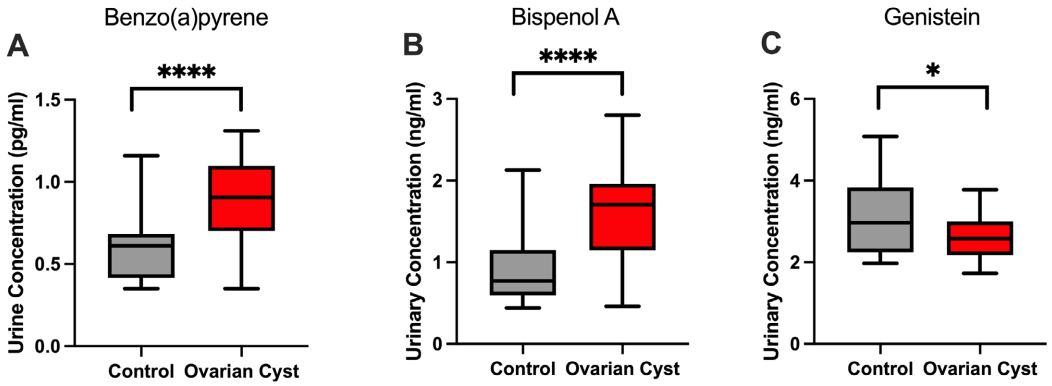


Figure 1. Comparison of the levels of endocrine disruptors in patients with ovarian cysts and normal controls. Single asterisk (*) represents P ≤ 0.05 and quadruple asterisk (****) represents P ≤ 0.001.

3.4. Association of EDCs with Pathological Ovarian Cysts

The results of binary logistic regression analysis in Figure 2 and Table 3 show

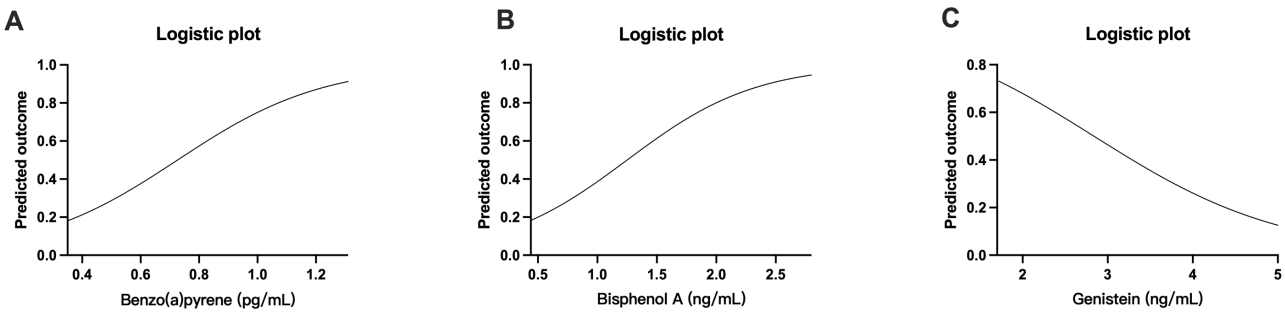


Figure 2. Binary regression analysis visualization of benzopyrene, bisphenol A and genistein with ovarian cysts.

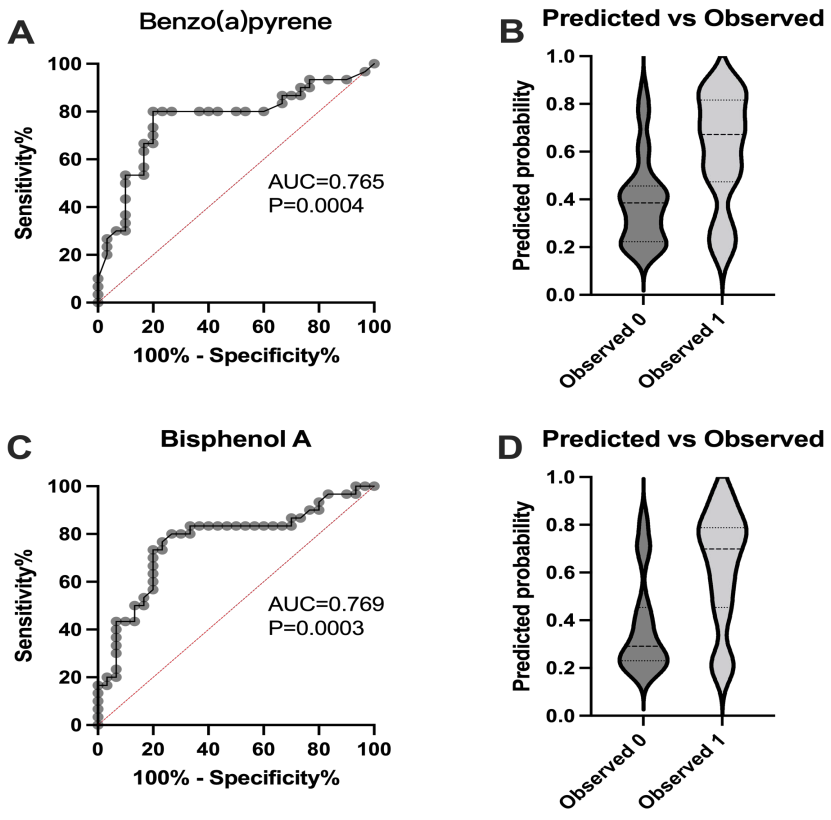
Table 3. Binary regression analysis of benzopyrene, bisphenol A and genistein with ovarian cysts.

B	S.E.	Wald	P-value	OR	95% lower	C.I. for OR upper
Benzopyrene (pg/mL) 4.171	1.483	7.913	0.005	64.799	3.543	1185.257
Bisphenol A (ng/mL) 2.263	0.664	11.611	0.001	9.609	2.615	35.312
Genistein (ng/mL) −1.879	0.692	7.378	0.007	0.153	0.039	0.593

that benzopyrene and bisphenol A are not only significantly associated with ovarian cysts. These results also show that the incidence of ovarian cysts was positively correlated to these independent risk factors, OR value reached 64.799 (P = 0.005) for benzopyrenes and 9.609 (P = 0.001) for bisphenol A. However, genistein was significantly negatively correlated with the incidence of ovarian cysts, and was an independent protective factor for ovarian cysts, with an OR value of 0.153 (P = 0.007).

3.5. Diagnostic Performance of Benzopyrene, Bisphenol A and Genistein on Ovarian Cysts

Evaluation of the diagnostic performance of benzopyrene, bisphenol A and genistein by ROC curve, the results show that the AUC of benzopyrene and bisphenol A reached 0.765 (P = 0.0004) and 0.769 (P = 0.0003), as a molecular marker of ovarian cysts, has good predictive screening performance. Genistein had the best diagnostic performance with an AUC of 0.649, but they had potential preventive and therapeutic effects on ovarian cysts (Figure 3).



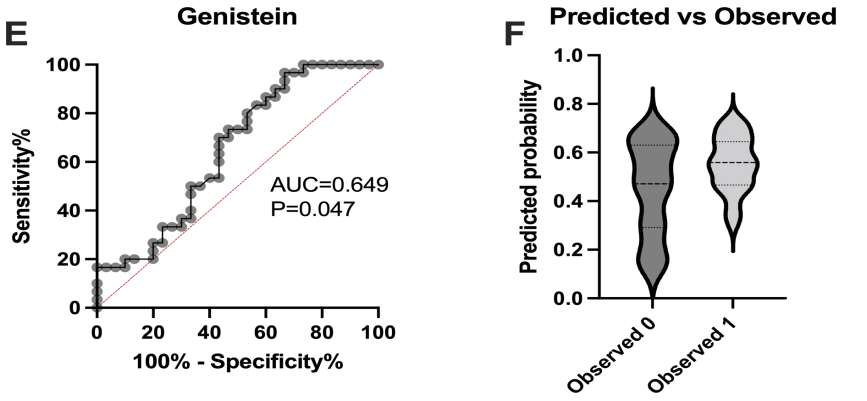


Figure 3. Diagnostic performance of benzopyrene, bisphenol A and genistein on ovarian cysts.

4. Discussion

Increasing evidence shows that endocrine-disrupting chemicals are involved in the development of various ovarian diseases like infertility, premature ovarian failure and abnormal sex steroid hormone levels, and also pose an increased risk for osteoporosis, depression, cardiovascular disease and early death [17] [18]. The occurrence of cardiovascular disease, depression and osteoporosis is attributed to abnormal sex steroid hormone levels caused by EDCs [12] [19]. Research has also shown that environmental exposures during fetal and early postnatal development can result in increased incidence of later life adult-onset health complications [20] [21] [22] [23].

In this study, we evaluated the concentration levels of EDCs namely Benzo(a)pyrene, Bisphenol A and Genistein between patients with pathological ovarian cysts and normal control group. We also assessed the predictive performance and association of Benzo(a)pyrene, Bisphenol A and Genistein Flavone with pathological ovarian cysts. To our knowledge, this is the first study to evaluate these relationships.

Patients in our study were older with mean age of 36.7 years similar to other studies previously done [24] [25]. Pathological ovarian cysts were common in postmenopausal women [26]. Majority of the pathological ovarian cysts were endometriomas (50%) similar to other studies [24].

The concentration levels of benzopyrene and bisphenol A in patients with ovarian cysts for our study were significantly higher than those in the normal control group, genistein was significantly higher in the control group. The reason could be that benzopyrene and bisphenol A may be risk factors for pathological ovarian cysts, while genistein may be a protective factor in the development of pathological ovarian cysts. Genistein is an isoflavone phytoestrogen found naturally in plants like soy beans, chickpeas, sunflower seeds and lentils [27]. Women are exposed to genistein primarily through ingestion of soy-based dietary products such as soy milk, tofu and soy flour [28] [29]. Bisphenol A is mainly found in polycarbonate resins namely plastic bags, bottles and packaging, particularly

water and milk bottles, coated tins, particularly food and drink cans, and microwave ovenware [30] [31] [32]. Women easily get exposed to benzopyrenes in coal tar, cigarette smoke, wood smoke and burn food [33].

Benzopyrene and bisphenol A were significantly associated with pathological ovarian cysts, incidence of pathological ovarian cysts was positively correlated to these EDCs, hence being independent risk factors for pathological ovarian cysts, the OR value reached 64.79 (P = 0.005) for benzopyrene and 9.609 (P = 0.001) for bisphenol A. However, genistein was negatively correlated with the incidence of pathological ovarian cysts, and was an independent protective factor for ovarian cysts, with an OR value of 0.153 (P = 0.007). This is similar to other previous findings as mentioned above that have shown how EDCs can cause alterations in the normal ovarian function thereby causing disease.

Evaluation of the diagnostic performance of benzopyrene, bisphenol A and genistein by ROC curve gave us an insight into how important these chemicals can be utilized as molecular biomarkers of pathological ovarian cysts. Significant results in our study have shown that the AUC for benzopyrene and bisphenol A reached 0.765 (P = 0.0004) and 0.769 (P = 0.0003) respectively. This means that benzopyrenes and bisphenol A maybe be important molecular markers of pathological ovarian cysts for predictive screening performances. Genistein had the best diagnostic performance with an AUC of 0.649, but also had potential preventive and therapeutic effects on pathological ovarian cysts.

5. Conclusion

Women are easily exposed to various kinds of EDCs which may significantly cause ovarian dysfunction from the fetal stage to adulthood. We observed that the concentration of benzopyrenes and bisphenol A was higher in patients with pathological ovarian cysts, and genistein was higher in normal controls. Benzopyrenes and bisphenol A were positively associated with pathological ovarian cysts. The evidence in our current study suggests that benzopyrene and bisphenol A might be potential novel predictive molecular biomarkers or be involved in the pathogenesis of pathological ovarian cysts while genistein may have preventive or may have inhibitory effects in the disease genesis. The present data suggest further in-depth research studies with large sample sizes for further validation of these effects. In the future, studies can be done to find specific molecular mechanisms through which benzopyrene and bisphenol A cause the pathogenesis of pathological ovarian cysts. More studies are also required to find mechanisms through which genistein inhibits pathological ovarian cyst development.

Ethics Approval and Consent to Participate

Consent to Participate

Approval of this study and waiving of the participants' informed consent due to the nature of the study were done by the ethics and research committee of the Second Affiliated Hospital of Nanjing Medical University. The data used in the

study were anonymized before its use. All methods were performed in accordance with the relevant guidelines.

Availability of Data and Materials

Data presented in this study can be provided upon request from the corresponding author. Due to public restrictions, data is not publicly available.

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Authors' Contribution

Concept and design were done by KC, XB and YXY. Statistical data analysis was done by SN. The original draft of the manuscript was done by KC. ZWW was involved in the interpretation of clinical data from the Chinese language to the English language. After the review of the manuscript content by all authors, it was agreed that the final version be submitted for publication.

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Conflicts of Interest

There are no conflicts of interest regarding the publication of this paper.

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Abbreviations

AUC—Area Under the Curve;
EDCs—Endocrine-Disrupting Chemicals;
OR—Odds Ratio;
P-value—Probability Value;
ROC Curve—Receiver Operating Characteristic Curve;
SD—Standard Deviation;
SPSS—Statistical Package for the Social Sciences.