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Exposure to Multiple Endocrine-Disrupting Chemicals and Associations with Female Infertility: A Case-Control Study

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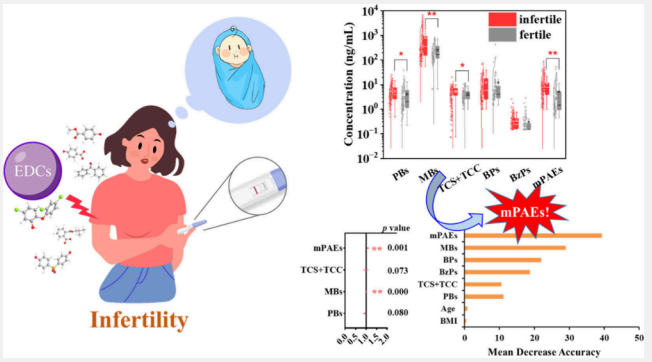
ABSTRACT: Parabens (PBs) and their metabolites (MBs), triclocarban (TCC), triclosan (TCS), bisphenols (BPs), benzophenones (BzPs), and phthalate metabolites (mPAEs) are typical endocrine-disrupting chemicals (EDCs) used in industrial production and daily life. Studies have suggested that these EDCs affect the reproductive system and may cause infertility; however, epidemiological evidence linking EDC exposure to infertility is still lacking. Herein, a total of 302 serum samples from women of reproductive age were collected, and six categories of typical EDCs were analyzed. The results revealed that EDCs are ubiquitous in female serum. The geometric mean (GM) concentrations of ∑PBs, ∑MBs, ∑(TCS+TCC), ∑BPs, ∑BzPs, and ∑mPAEs were 3.36, 297, 3.87, 4.39, 0.257, and 4.56 ng/mL, respectively. The serum concentrations of ∑PBs, ∑MBs, ∑(TCS+TCC), and ∑mPAEs from infertile women (GM: 4.16, 397, 4.01, and 7.33, respectively) were higher than those from fertile women (2.45, 192, 3.65, and 2.27, respectively) ($p < 0.05$). The results of binary logistic regression and random forest suggest that mPAEs, such as mBP/miBP and mEHP, may contribute to infertility. This study provides insight into the relationship between the EDC exposure and reproductive outcomes.



KEYWORDS: *Endocrine-disrupting chemicals, Human exposure, Female infertility, Serum, Association*

1. INTRODUCTION

Infertility is usually defined as the inability to conceive after one year of regular and unprotected sexual intercourse.[1] Previous estimates of infertility prevalence suggested that the number of couples suffering from infertility was 48.5 million globally, and the number of married women with infertility was 186 million in developing countries.[2] Genetic, environmental, and behavioral factors can cause female infertility, with environmental and lifestyle factors likely to play a more significant role in increasing infertility.[3]

Endocrine-disrupting chemicals (EDCs) are ubiquitous environmental pollutants. Studies have found that EDCs can bind to estrogen in organisms and may cause adverse effects on reproduction and homeostasis.[4−8] For instance, exposure to low doses of triclosan (TCS) and triclocarban (TCC) can disrupt the estrogen system, with TCC exhibiting higher agonistic activity than TCS.[9] The chemical 2,2′,4,4′-tetrahydroxybenzophenone (BP-2) has been shown to significantly inhibit oocyte development in exposed females, and their ovaries have much fewer mature and more atretic follicles.[10] Exposure to mono (2-ethylhexyl) phthalate (mEHP) results in oocyte degeneration and failure of oocyte maturation.[11] Overall, the evidence has demonstrated that exposure to EDCs can negatively affect reproductive health in both animals and humans and may further contribute to infertility problems.

EDCs have been repeatedly detected in female serum,[12,13] urine,[13−16] amniotic fluid,[13] follicular fluid,[14] and placental tissue.[17,18] Some studies involving animal experiments, as well as results from epidemiological studies, support the conclusion that EDCs may have adverse effects on female fertility. Previous studies have shown that compounds from multiple chemical classes (e.g., parabens, TCS, bisphenol A (BPA), and phthalates) affect reproductive endocrine balance and are linked to an increased risk of female infertility.[19,20] Epidemiological and experimental evidence suggests that BPA can affect the expression of reproduction-related genes and epigenetic modification, which are strongly linked to infertility.[21] Urinary BPA concentrations are associated with decreased antral follicle counts and reduced oocyte retrieved counts in women undergoing fertility treatment.[22,23] A cross-

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sectional study on females in the United States found that the combination of 2-hydroxy-4-methoxy benzophenone (BP-3), BPA, and TCS was significantly associated with the occurrence of female infertility.[3] However, the adverse health consequences of exposure to EDCs reported in current studies remain uncertain and controversial.

In this study, serum samples from women of reproductive age (infertile: 181, fertile: 121) were collected. Six categories of typical EDCs (n = 36), including parabens (PBs), paraben metabolites (MBs), TCS, TCC, bisphenols (BPs), benzophenones (BzPs), and phthalate metabolites (mPAEs), were analyzed. EDC concentrations in serum samples of infertile and fertile women were compared. Additionally, machine learning algorithms such as logistic regression and random forest were applied to explore the risk factors associated with infertility. This study aims to fill the knowledge gap regarding the association between EDCs and female infertility and to provide new data on whether EDC exposure in women leads to reproductive damage.

2. MATERIALS AND METHODS

2.1. Materials and Chemicals

Information on native and mass-labeled EDC standards and reagents in this study is provided in detail in the Supporting Information (Text S1 and Table S1).

2.2. Study Population

In this case-control study, the inclusion criteria for all enrolled women were as follows: women of reproductive age (20−45 years old) with no bad lifestyle habits such as smoking or alcohol consumption. Each participant was informed about this investigation and signed an informed consent form before sample collection. Venous samples were collected within 2−4 days of menstruation. Relevant information was collected, including age, height, and weight. Infertility is usually defined as the inability to conceive after one year of regular and unprotected sexual intercourse. All personnel who provided serum samples had a clinical diagnosis at Beijing Obstetrics and Gynecology Hospital affiliated, Capital Medical University in 2021. This study was approved by the Ethics Committee of the Obstetrics and Gynecology Hospital affiliated, Capital Medical University (2021-KY-001-01). Cases of infertility associated with chronic diseases, infections, structural abnormalities of the uterus, or poor paternal health status were excluded from the study. A total of 302 serum samples were retained, including 181 infertile women and 121 controls. Each 5 mL venous blood was collected in a medical serum tube, kept at room temperature for 30 min, centrifuged at 1800g for 10 min, and transferred to a 2.0 mL glass vial. After collection, all serum samples were kept at −80 °C until they were analyzed. Further details regarding the samples are available in Table S2.

2.3. Sample Preparation and Instrumental Analysis

The analytical procedures for the determination of 36 EDCs in serum were based on liquid−liquid extraction and solid-phase extraction, as shown in Text S2. Ultraperformance liquid chromatography coupled with quadrupole mass spectrometry (UPLC-MS/MS) was used for instrumental analysis. The optimized MS/MS parameters for target analytes are shown in Text S3 and Table S3.

2.4. Quality Assurance and Quality Control (QA/QC)

The procedural blanks, recoveries, standard curves, limits of detection, and limits of quantification are listed in Text S4, Table S4, and Table S5. Information on data analysis is listed in Text S5.

3. RESULTS AND DISCUSSION

3.1. Characteristics of Subjects

Table S2 shows the sociodemographic characteristics of subjects (n = 302) in the study. The median age of infertile women was 33.0 years [interquartile range (IQR): 30.0−37.0] and that of fertile women was 32.0 years (IQR: 29.8−35.0). Body mass index (BMI) is an important parameter for determining the degree of obesity and the basic health status of a human being. The World Health Organization (WHO) standard for BMI for healthy adults is 18.5−25.0 kg/m^2.[24] The median BMI of infertile women was 21.0 kg/m^2, with 7.73% being obese or severely obese, while the median BMI of fertile women was 21.2 kg/m^2, with 2.02% being obese or severely obese.

3.2. Concentration and Composition Profiles of EDCs in Female Serum

The concentrations of EDCs, including parabens, paraben metabolites, TCS, TCC, bisphenols, benzophenones, and phthalate metabolites, were measured in female serum. Their total concentrations were presented as ∑PBs, ∑MBs, ∑(TCS +TCC), ∑BPs, ∑BzPs, and ∑mPAEs, respectively. The values of min, max, geometric mean (GM), and median are listed in Table 1. The composition profiles of EDCs in serum are shown in Figure S1. MBs were the main contributor, accounting for 92.3% of the total EDC concentrations, followed by mPAEs (2.38%), BPs (2.01%), TCS+TCC (1.85%), PBs (1.40%), and BzPs (0.085%).

3.2.1. Parabens. MeP was found in 100% of the samples. The detection rates of EtP, BuP, and HepP were 95.7%, 45.4%, and 21.9%, respectively. BzP was not found in any sample. MeP was more abundant in serum samples, followed by EtP, collectively accounting for 99.4% of the total paraben concentration (Figure 1). A similar composition profile in serum has been reported in previous studies,[13,25] possibly because MeP is the main paraben analog added to personal care and cosmetic products.[26] A previous study showed that parabens were widely detected in personal care products (n = 108) sampled from Wuhan City, China. MeP was the most frequently found compound, particularly in 100% of the body lotion, 94% of the face cream, 100% of the body wash, 100% of the hand cream, 100% of the mouthwash, and 100% of the eyewash. Among the paraben analogs, MeP has also been found to have the highest concentration in personal care and cosmetic products (e.g., body lotion, toner, facial cream, and facial cleanser).[26] The GM concentrations of MeP and EtP (3.05 and 0.185 ng/mL) in this study were lower than those observed in India population (9.85 and 2.27 ng/mL),[27] and comparable to those of pregnant women from several Chinese provinces (1.86 and 0.239 ng/mL).[25]

3.2.2. Paraben Metabolites. The serum samples were also examined for paraben metabolites (OH-MeP, OH-EtP, and 4-HB). The detection rates of ∑MBs, 4-HB, OH-MeP, and OH-EtP in serum samples were 99.7%, 99.3%, 65.2%, and 76.2%, respectively. The concentration of 4-HB in serum was up to 6700 ng/mL. The 4-HB concentration (GM: 296 ng/mL) was approximately 3 orders of magnitude higher than those of OH-MeP (0.150 ng/mL) and OH-EtP (0.122 ng/mL) and 2−3 orders of magnitude higher than those of its parent compound (MeP: 3.05 ng/mL, EtP: 0.185 ng/mL). It should be noted that OH-MeP and OH-EtP are MeP and EtP-specific metabolites, respectively, whereas 4-HB is not a specific biomarker for exposure to individual parabens.[28] Both animal and human studies have shown that several parabens can be transformed to a common metabolite, i.e., 4-HB.[29] This may explain why 4-HB concentration was higher than other paraben metabolites. Our results indicated that the GM

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Table 1. Concentrations (ng/mL) of EDCs in Serum Samples from Infertile and Fertile Women[a]

	Infertile (n = 181)					Fertile (n = 121)					All (n = 302)				
	DR(%)	Min	Max	GM	Median	DR (%)	Min	Max	GM	Median	DR (%)	Min	Max	GM	Median
Parabens															
MeP	100	0.460	24.8	3.77	3.39	100	0.182	38.7	2.22	1.89	100	0.182	38.7	3.05	2.92
EtP	97.8	<LOQ	4.39	0.232	0.268	92.6	<LOQ	1.04	0.132	0.161	95.7	<LOQ	4.39	0.185	0.223
BuP	55.2	<LOQ	4.15	0.019	0.014	30.6	<LOQ	0.116	0.012	<LOQ	45.4	<LOQ	4.15	0.016	<LOQ
HepP	29.3	<LOQ	0.113	0.009	<LOQ	10.7	<LOQ	0.084	0.007	<LOQ	21.9	<LOQ	0.113	0.008	<LOQ
BzP	0	<LOQ	<LOQ	<LOQ	<LOQ	0	<LOQ	<LOQ	<LOQ	<LOQ	0	<LOQ	<LOQ	<LOQ	<LOQ
∑PBs	100	0.496	25.1	4.16	3.89	100	0.218	39.2	2.45	2.05	100	0.218	39.2	3.36	3.21
Paraben metabolites															
4-HB	100	56.7	6700	396	345	98.3	<LOQ	809	192	170	99.3	<LOQ	6700	296	261
OH-MeP	74.0	<LOQ	2.65	0.166	0.148	52.1	<LOQ	4.03	0.128	0.081	65.2	<LOQ	4.03	0.150	0.114
OH-EtP	78.5	<LOQ	3.2	0.129	0.116	72.7	<LOQ	4.35	0.112	0.084	76.2	<LOQ	4.35	0.122	0.104
∑MBs	100	56.7	6700	397	345	99.2	<LOQ	817	192	170	99.7	<LOQ	6700	297	261
TCS/TCC															
TCS	98.9	<LOQ	20.1	3.99	5.50	100	0.988	11.4	3.65	3.61	99.3	0.068	20.1	3.85	4.61
TCC	14.9	<LOQ	0.800	0.007	<LOQ	5.79	<LOQ	0.332	<LOQ	<LOQ	11.3	<LOQ	0.800	0.006	<LOQ
∑(TCS+TCC)	98.9	0.073	20.1	4.01	5.51	100	0.993	11.4	3.65	3.63	99.3	<LOQ	20.1	3.87	4.62
Bisphenols															
BPF	8.84	<LOQ	1.12	0.116	<LOQ	7.44	<LOQ	0.828	0.116	<LOQ	8.28	<LOQ	1.12	0.116	<LOQ
BPA	95.0	<LOQ	63.4	2.83	3.35	100	<LOQ	114	2.67	2.26	97.0	<LOQ	114	2.76	2.57
BPB	11.0	<LOQ	8.82	0.490	<LOQ	10.7	<LOQ	2.84	0.477	<LOQ	10.9	<LOQ	8.82	0.485	<LOQ
BPS	33.7	<LOQ	35.8	0.066	<LOQ	92.6	<LOQ	417	0.276	0.197	57.3	<LOQ	417	0.117	0.096
BPZ	2.21	<LOQ	0.285	0.059	<LOQ	1.65	<LOQ	0.145	0.058	<LOQ	1.99	<LOQ	0.285	0.059	<LOQ
BPAP	1.66	<LOQ	0.501	0.098	<LOQ	9.09	<LOQ	0.564	0.104	<LOQ	4.64	<LOQ	0.564	0.100	<LOQ
BPP	1.10	<LOQ	3.49	0.045	<LOQ	1.65	<LOQ	0.095	0.044	<LOQ	1.32	<LOQ	3.49	0.045	<LOQ
∑BPs	96.7	<LOQ	65.9	4.45	4.47	100	1.45	440	5.38	4.04	98.0	<LOQ	422	4.39	3.90
Benzophenones															
BP-1	34.8	<LOQ	0.249	0.012	<LOQ	15.7	<LOQ	0.207	0.010	<LOQ	27.2	<LOQ	0.249	0.011	<LOQ
BP-2	0	<LOQ	<LOQ	<LOQ	<LOQ	0	<LOQ	<LOQ	<LOQ	<LOQ	0	<LOQ	<LOQ	<LOQ	<LOQ
BP-8	26.0	<LOQ	0.366	0.039	<LOQ	14.0	<LOQ	0.337	0.034	<LOQ	21.2	<LOQ	0.366	0.037	<LOQ
4-OH-BP	31.5	<LOQ	1.01	0.015	<LOQ	14.9	<LOQ	0.525	0.013	<LOQ	24.8	<LOQ	1.01	0.014	<LOQ
BP-3	58.6	<LOQ	2.39	0.178	0.158	34.7	<LOQ	2.62	0.148	<LOQ	49.0	<LOQ	2.62	0.165	<LOQ
∑BzPs	79.6	0.152	2.61	0.278	0.240	42.1	0.152	2.87	0.229	0.152	64.6	<LOQ	2.87	0.257	0.206
Phthalate metabolites															
mMP	99.4	<LOQ	16.2	1.40	1.66	100	0.105	11.3	0.964	0.888	99.7	<LOQ	16.2	1.21	1.22
mEP	61.9	<LOQ	32.0	0.122	0.107	44.6	<LOQ	24.5	0.064	<LOQ	55.0	<LOQ	32.0	0.094	0.057
mCPP	1.66	<LOQ	0.422	0.043	0.042	0	<LOQ	0.042	0.042	<LOQ	0.99	<LOQ	0.422	0.042	<LOQ
mBP/miBP	81.8	<LOQ	8.06	0.525	1.11	38.0	<LOQ	6.09	0.043	<LOQ	64.2	<LOQ	8.06	0.193	0.428
mECPP	1.66	<LOQ	0.358	0.025	<LOQ	0	<LOQ	0.024	0.024	<LOQ	0.99	<LOQ	0.358	0.024	<LOQ
mEOHP	15.5	<LOQ	1.30	0.022	<LOQ	5.79	<LOQ	0.112	0.020	<LOQ	11.6	<LOQ	1.30	0.021	<LOQ
mEHHP	9.94	<LOQ	0.270	0.017	<LOQ	6.61	<LOQ	0.121	0.016	<LOQ	8.61	<LOQ	0.270	0.016	<LOQ
mCHP	13.3	<LOQ	1.96	0.033	<LOQ	6.61	<LOQ	0.711	0.027	<LOQ	10.6	<LOQ	1.96	0.030	<LOQ
mBzP	8.84	<LOQ	0.100	0.010	<LOQ	4.13	<LOQ	0.114	0.009	<LOQ	6.95	<LOQ	0.114	0.009	<LOQ

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Table 1. continued

	Infertile (n = 181)					Fertile (n = 121)					All (n = 302)				
	DR(%)	Min	Max	GM	Median	DR (%)	Min	Max	GM	Median	DR (%)	Min	Max	GM	Median
mEHP	66.9	<LOQ	42.4	1.23	2.67	24.0	<LOQ	26.0	0.229	<LOQ	49.7	<LOQ	42.4	0.627	<LOQ
mOP	32.0	<LOQ	41.1	0.154	<LOQ	13.2	<LOQ	20.6	0.063	<LOQ	24.5	<LOQ	41.1	0.107	<LOQ
mCMHP	21.0	<LOQ	0.486	0.029	<LOQ	15.7	<LOQ	0.142	0.026	<LOQ	18.9	<LOQ	0.486	0.027	<LOQ
mNP	4.42	<LOQ	3.25	0.025	<LOQ	31.4	<LOQ	0.372	0.035	<LOQ	15.2	<LOQ	3.25	0.029	<LOQ
∑mPAEs	100	0.960	87.7	7.33	7.82	100	0.445	53.8	2.27	1.49	100	0.445	87.7	4.56	5.31

[a]DR = detection rate (%), GM = geometric mean, and LOQ = limit of quantification.

concentrations of 4-HB (296 ng/mL) in serum in this study were comparable to those of pregnant women from several Chinese provinces (211 ng/mL).[25]

3.2.3. TCS/TCC. ∑(TCS+TCC) were detected widely in serum samples with a detection rate of 99.3%, suggesting that women of reproductive age widely used these chemicals. The serum concentration of TCS (GM: 3.85 ng/mL, range: 0.068−20.1 ng/mL) was 3 orders of magnitude higher than that of TCC (0.006 ng/mL, < LOQ-0.800 ng/mL), which indicates that women may use TCS more frequently than TCC. In 2015, the National Medical Products Administration has restricted the use of TCS and TCC in cosmetic products, with the thresholds being 0.3% for TCS and 0.2% for TCC,[30] suggesting that the concentrations of TCS in cosmetic products may be higher than those of TCC. Our results on the GM concentration of TCS (3.85 ng/mL) was higher than that of pregnant women from Beijing, China (fetal anomaly group: 0.191 ng/mL, control group: 0.110 ng/mL),[31] and comparable to those of Chinese pregnant women (1.00 ng/mL),[25] (1.10 ng/mL),[32] and Indian pregnant women (7.15 ng/mL).[27] The concentration of TCC in our results (0.006 ng/mL) was comparable to those of Chinese pregnant women (0.005 ng/mL),[25] but lower than those of pregnant women from Beijing, China (fetal anomaly group: 0.059 ng/mL, control group: 0.081 ng/mL).[31]

3.2.4. Bisphenols. The detection rates were ranked as follows: BPA (97.0%), BPS (57.3%), BPB (10.9%), BPF (8.28%), BPAP (4.64%), BPZ (1.99%), and BPP (1.32%), respectively. These results were in line with the detection rates reported by an earlier investigation for human serum, with BPA having the highest detection rate.[33] The GM serum concentrations of BPA, BPS, BPB, BPF, BPAP, BPZ, and BPP were 2.76, 0.117, 0.485, 0.116, 0.100, 0.059, and 0.045 ng/mL, respectively. The major bisphenol used was BPA (87.2%), followed by BPS (9.04%), collectively accounting for 96.2% of ∑BPs (Figure 1). BPS is widely used as a primary replacement for BPA. For example, Liao et al. found that BPS has been extensively detected in human urine from the United States and seven Asian countries.[34] China is the world's biggest producer and consumer of BPA. The production and consumption of BPA was 1,430,000 tons and 1,293,000 tons, accounting for 20.0% and 23.2% of global BPA production and consumption, respectively.[35,36] Additionally, China's BPA consumption increased gradually, reaching 309,500 tons, 724,300 tons, 1,306,400 tons, and 1,550,000 tons in 2005, 2010, 2016, and 2017, respectively.[36] The large production capacity and consumption amount of BPA might affect its congener profile in serum. These results indicate that the congener profile of BPs in serum is consistent with that found in other environmental matrices, such as foodstuff,[37] sediment,[38] and indoor air.[39] For example, the mean contribution of BPA to ∑BP concentrations in foodstuffs collected from nine cities in China was 64%. BPF and BPS accounted for 10% and 7.7% of the ∑BP concentrations, respectively.[37] The concentration of BPA (GM: 2.76 ng/mL) in this study was comparable to that from India (5.83 ng/mL)[27] and 1−2 orders of magnitude greater than that from Tianjin, China (0.10 ng/mL)[40] and Japan (0.051 ng/mL).[41] Gao et al. reported that BPA was found in adult serum in a densely industrialized region from Bao'an, Shenzhen, China, at a high GM concentration of 44.4 ng/mL, which is significantly higher than our results (2.76 ng/mL).[33]

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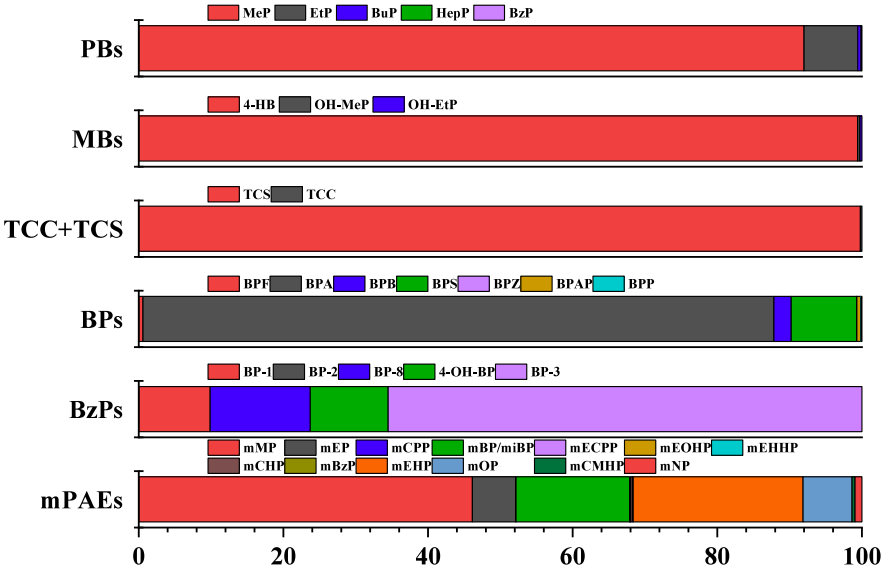

Figure 1. Composition profiles of parabens, paraben metabolites, TCS, TCC, bisphenols, benzophenones, and phthalate metabolites in serum samples.

3.2.5. Benzophenones. In general, compared to other EDCs, ∑BzPs showed a low detection rate (64.6%) and concentration (GM: 0.257 ng/mL). The detection rates of BP-1, BP-8, 4-OH-BP, and BP-3 were 27.2%, 21.2%, 24.8%, and 49.0%, respectively, while BP-2 was not detected in any sample. BP-3, the most commonly used ultraviolet filter, can be found in a wide range of daily use products, including sunscreens, skin creams, cosmetics, and hair spray.[42] Concerning the harmful effects, the usage of such products containing BP-3 is not high for women who are pregnant or preparing for pregnancy. As shown in Figure 1, BP-3 was the main compound of ∑BzPs (65.5%), followed by BP-8 (13.8%), 4-OH-BP (10.8%), and BP-1 (9.87%). The BP-3 concentration (GM: 0.165 ng/mL) was almost 5−16 times higher than that of the other four BzPs (<LOQ−0.037 ng/mL), possibly due to its high yield and concentration in the environment.[43] The concentration of BP-3 (GM: 0.165 ng/mL) in this study was comparable to those of women from Guangzhou, China (0.10 ng/mL)[44] and Tianjin, China (0.38 ng/mL).[45] The content of 4-OH-BP (0.014 ng/mL) was lower than that of pregnant women from Tianjin, China (0.67 ng/mL)[45] and higher than that of women from Guangzhou, China (<0.02 ng/mL).[44]

3.2.6. Phthalate Metabolites. ∑mPAEs were detected widely in serum samples with detection rates of 100%. The detection rates of mMP, mEP, and mEHP in serum samples were 99.7%, 55.0%, and 49.7%, respectively. The chemicals of mCPP, mECPP, mEHHP, and mBzP were only found in a few samples (detection rate <10%). In another cross-sectional study of male urine, all mPAEs were detected in 90% of the samples, except for mOP.[46] In serum samples, mMP was the most prevalent (46.1%), followed by mEHP and mBP/miBP (23.5% and 15.7%, respectively) (Figure 1), which were similar to those found in human serum and whole blood from Quzhou, China.[12] It may be explained by the large production and wide consumption of their parent compounds (e.g., DEHP, DBP, DIBP, and DMP) in daily life.[47] In a previous study, mBP and miBP were the main contributing compounds, totally accounting for 69.0% of ∑mPAEs.[48] The chemicals mCMHP and mECPP were also the predominant congeners,[48] but they were detected less in this study. The mMP concentration (GM: 1.21 ng/mL) is close to that found in maternal serum in Tianjin, China (1.27 ng/mL).[48]

3.3. Differences in Serum Concentrations of EDCs in Infertile and Fertile Women

Concentrations of EDCs in serum samples from infertile and fertile women were compared (Figure 2). Higher concentrations of ∑PBs were found in serum from infertile women (GM: 4.16, range: 0.496−25.1 ng/mL) as compared to concentrations found in fertile women (2.45, 0.218−39.2) ($p < 0.05$). The concentrations of MeP and EtP in infertile women (GM: 3.77 and 0.232 ng/mL, respectively) were also observed to be higher than those in fertile women (2.22 and 0.132 ng/mL, respectively) ($p < 0.05$ and $p < 0.01$, respectively). The detection rates of ∑MBs in infertile and fertile women were 100% and 99.2%, respectively. The GM concentration of 4-HB (396 ng/mL) from infertile women was two times higher than that found for fertile women (192 ng/mL) ($p < 0.01$). GM concentrations of OH-MeP and OH-EtP (0.166 and 0.129 ng/mL) were comparable to those in fertile women (0.128 and 0.112 ng/mL).

There were differences in serum concentrations of ∑(TCS +TCC) between the infertile and fertile women ($p < 0.05$). TCS was frequently detected in serum samples from infertile and fertile women, with detection rates of 98.9% and 100%, respectively. Low detection rates of TCC (14.9% and 5.79%) were observed in samples from infertile and fertile women. The predominant compound in the two groups was TCS, with higher GM concentration from infertile women (3.99 ng/mL) than fertile women (3.65 ng/mL) ($p < 0.05$). This suggests TCS may be associated with the occurrence of female infertility, which is similar to the results of the association between urinary TCS concentrations and infertility among U.S. women.[3]

The GM concentrations of ∑BPs in serum from infertile and fertile women were 6.77 and 5.38 ng/mL, respectively. Between infertile and fertile women, there was no significant difference in the concentrations of ∑BPs ($p > 0.05$). BPS concentration in serum from infertile women (GM: 0.066 ng/

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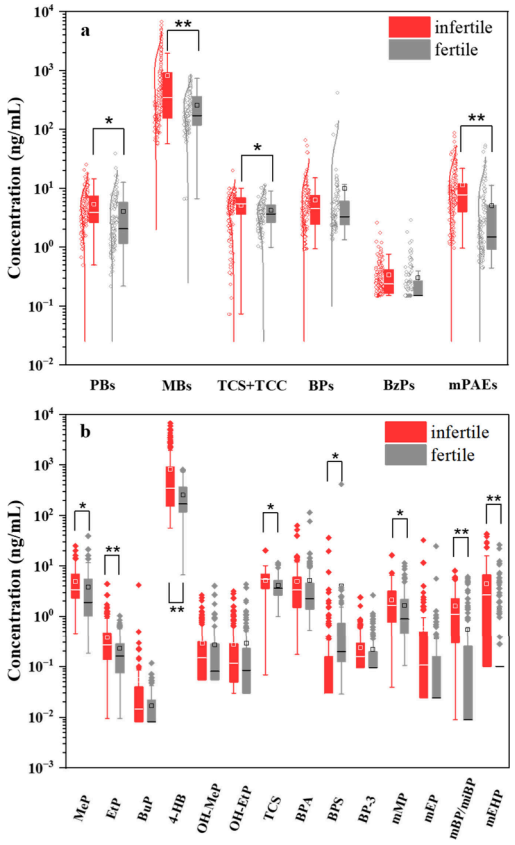

Figure 2. (a) Concentrations of parabens (PBs), paraben metabolites (MBs), TCS, TCC, bisphenols (BPs), benzophenones (BzPs), and phthalate metabolites (mPAEs) in serum from infertile and fertile women. (b) Concentrations of individual EDCs in serum from infertile and fertile women. The lower whisker, bottom edge of the box, top edge of the box, and upper whisker represent the 5th, 25th, 75th, and 95th percentile of concentrations, respectively, and the lower and upper stars denote the 1st and 99th percentile of concentrations, respectively. The open square and the line within the box stand for the mean and median concentrations, respectively. *: $p < 0.05$, **: $p < 0.01$.

mL) was lower than that found in serum from fertile women (0.276 ng/mL) ($p < 0.05$). Studies have shown that many factors contribute to the differences in bisphenol concentrations, including the economic level. Investigations have verified a positive correlation between financial status and industrial or personal care product use.[49] Two of our previous studies have also shown that the economic level affects the concentrations of BPs in urine in local populations.[50,51] Research on the key factors affecting BPS concentrations in serum needs to be clarified in further studies. In contrast, comparable concentrations of BPA were found in infertile women (GM: 2.83 ng/mL) and fertile women (2.67 ng/mL). Animal and epidemiological studies have shown that BPA affects reproductive endocrine balance and fertility.[19,21] According to Arya et al., there is a significant correlation between BPA and the occurrence of female infertility.[3] However, these results are inconsistent, highlighting the need for further validation research.

The detection rate of ∑BzPs in serum samples from infertile women (79.6%) was higher than that of fertile women (42.1%), but their GM concentrations were comparable in infertile (0.278 ng/mL) and fertile women (0.229 ng/mL). This result is in line with the findings of earlier studies.[52,53] In a long-term animal experiment, rats were exposed to BP-3 by daily feeding of a diet containing BP-3, and no reproductive toxicological effects were found even at the highest concentration of 2000 mg/kg.[52] Ma et al. summarized the current studies on the reproductive toxicity of BzPs and suggested that only 2,2′,4,4′-tetrahydroxyl benzophenone and 2-hydroxyl-4-methoxyl benzophenone may endanger the reproductive capacities of human and animal.[53]

The concentrations of ∑mPAEs in serum samples from infertile women ranged from 0.960 to 87.7 ng/mL, and the concentration range in control group women was 0.445−53.8 ng/mL. Serum samples collected from infertile women contained a higher concentration of mMP, mBP/miBP, and mEHP ($p < 0.05$, $p < 0.01$, and $p < 0.01$, respectively), with GM values of 1.40, 0.525, and 1.23 ng/mL, respectively.

Taken together, the total concentrations of EDCs found in serum from infertile women were higher than those found in fertile women, suggesting the potential for higher exposure to humans. This might reveal that EDCs are associated with female infertility.

3.4. Identification of Risk Factors Associated with Infertility

In epidemiologic studies, findings have been inconsistent regarding the associations between EDC exposure and infertility. This inconsistency may be due to a variety of factors, including differences in demographic characteristics, sample size, study design, and EDC distributions. The associations between serum levels of EDCs and the risk of infertility were analyzed by binary logistic regression (Figure 3). Out-of-bag (OOB) error, accuracy, and AUC were used to assess the stability and performance of the random forest models. For EDC classes, the OOB error, accuracy, and AUC were 15.17%, 0.913, and 0.875, respectively. For individual EDCs, the OOB error, accuracy, and AUC were 3.08%, 1, and 1, respectively. The odds ratios (ORs) and their corresponding 95% confidence intervals (CI) were calculated. Variables, including clinical factors (e.g., age and BMI) and individual EDCs (DR: ≥40%) with significant differences were screened. Factors with OR > 1 indicate they are risk factors for infertility. The results showed that mPAEs (OR = 1.079, $p < 0.01$) and MBs (OR = 1.002, $p < 0.01$) were risk factors for infertility, and exposure to these two classes of EDCs may be associated with infertility. In addition, individual compounds (DR: ≥40%) were chosen for analysis. The results showed that mEHP (OR = 1.312, $p < 0.01$), mBP/miBP (OR = 1.674, $p < 0.01$), and 4-HB (OR = 1.002, $p < 0.01$) were risk factors for infertility. The relative importance of EDCs was further analyzed using a random forest model (Figure 4). The contributions of various variables decrease as the prediction accuracy decreases. As shown in Figure 4a, mPAEs and MBs were the major features of the random forest model, which aligned with the results of binary logistic regression analysis. For individual EDCs (Figure 4b), the results showed that the top four, in descending order, were mBP/miBP, mEHP, TCS, and 4-HB, supporting the idea that exposure to mPAEs poses a certain risk of infertility. Toxicological studies have demonstrated the reproductive effects of mPAEs. They can affect folliculogenesis, oocyte maturation, and embryo development, leading to reduced fertility. mBP is the major metabolite of DBP and has been found in more than 90% of human follicular fluid samples. Growth inhibition occurred at ≥10 μg/mL of

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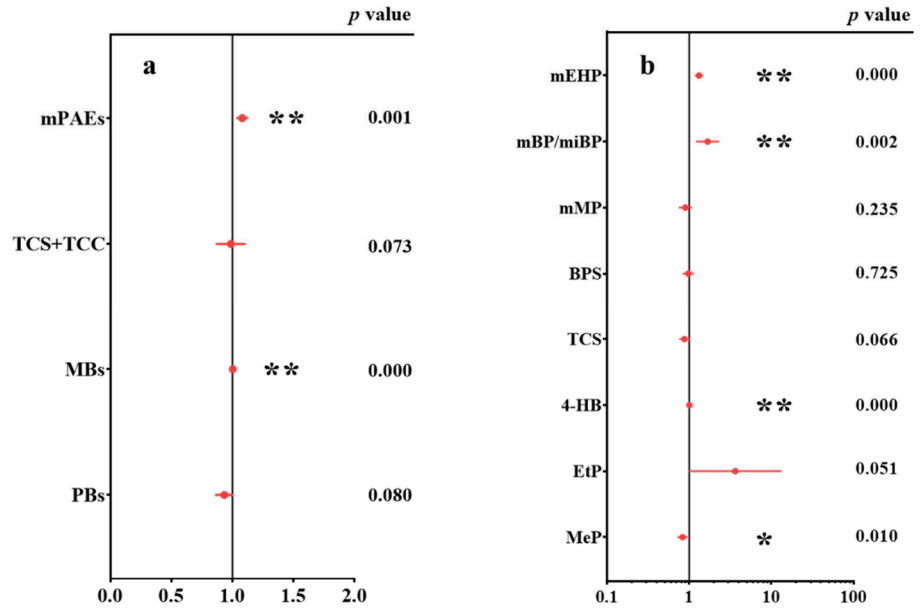

Figure 3. Associations between serum levels of EDCs and the risk of infertility by binary logistic regression: (a) for EDC classes and (b) for individual EDCs (*$p < 0.05$; **$p < 0.01$).

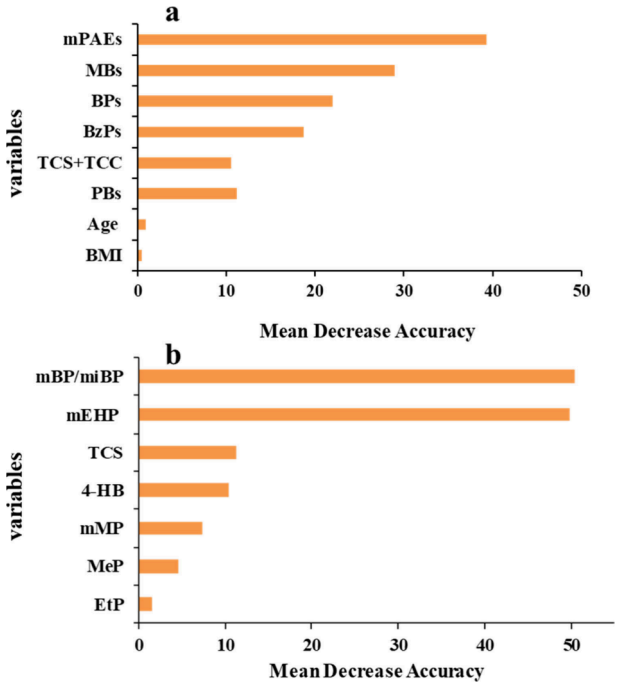

Figure 4. Variable importance obtained from the mean decrease accuracy for infertility: (a) for EDC classes and (b) for individual EDCs.

DBP exposure, and cytotoxicity occurred at ≥500 μg/mL. These results imply that antral follicles are negatively impacted by the DBP concentrations of 10 μg/mL or higher.[54] In a previous study, exposure to mEHP in porcine oocytes was found to result in oocyte degeneration and failure of oocyte maturation.[11] According to Hannon et al., mEHP directly stimulated early folliculogenesis while inhibiting the synthesis of steroid hormones. In neonatal ovaries, mEHP could result in a decrease in germ cells and an increase in primary follicles.[55] Molecular docking studies indicate structural similarities between mPAEs (e.g., mEHHP, mEOHP, mECPP, and mCMHP) and the native ligand testosterone. They can disrupt androgen receptor signal transduction and may eventually induce androgen-related reproductive dysfunction.[56] Despite low detection rates and concentrations, BzPs ranked fourth in the reproductive toxicity in the random forest model. BP-1, the metabolite of BP-3, has adverse effects on female reproduction. A recent review summarized that BP-1 caused a strong estrogenic response *in vivo* by an uterotrophic test. In all studies regarding BP-1, uterine weights increased statistically significantly at doses of 300−1000 mg/kg bw/day. However, statistically significant increases were not observed in most uterotrophic studies with BP-3.[57]

4. ENVIRONMENTAL IMPLICATIONS

This study found that women of reproductive age were exposed to at least two EDCs at the same time, and the detection rate of parabens and phthalate metabolites in serum reached 100%. Among the six types of EDCs, the contributions from high to low are in the order: ∑MBs (92.3%) > ∑mPAEs (2.38%) > ∑BPs (2.01%) > ∑TCS+TCC (1.85%) > ∑PBs (1.40%). The important contributed compounds in each type of pollutant were consistent with those found in previous studies. MeP, TCC, 4-HB, BPA, BP-3, and mMP were the predominant compounds in different EDC classes. The serum concentrations of ∑PBs, ∑MBs, ∑TCS+TCC, and ∑mPAEs from infertile women were higher than those from fertile women. Further analysis indicated that mPAEs, such as mBP/miBP and mEHP, were risk factors for infertility. However, certain limitations exist in this study. First, there is a need to establish more rigorous inclusion criteria for the case-control group. For example, considering the application of specific target compounds in medications, women who are taking medication need to be excluded. Additionally, women who have recently been diagnosed with infertility and have not undergone hormone or medication treatments could be considered as cases. This would allow for further investigations into the relationship between daily exposure to EDCs and endocrine hormone levels, as well as the association between endocrine hormone levels and infertility. Second, compared to

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the single measurement in this study, implementing longitudinal sampling from individual participants would avoid the temporal variability of EDCs in serum and reflect relatively long-term exposure levels. Lastly, further animal experiments are needed to reinforce the findings derived from the case-control study.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/envhealth.4c00040.

Texts: chemicals and reagents, sample preparation, instrumental analysis, QA/QC, and data analysis in this study; tables: a description of the structure and properties of target analytes, sociodemographic characteristics of the subjects, optimized MS/MS parameters, recoveries, limits of detection, and limits of quantitation for target analytes; figures: composition profiles of target EDCs (PDF)

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Notes

The authors declare no competing financial interest.

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