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# Association of organophosphate flame retardant metabolite concentrations in follicular fluid with in vitro fertilization outcomes among infertile women

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ABSTRACT

Organophosphorus flame retardants (OPFRs) are widely used endocrine-disrupting chemicals; however, the influence of OPFRs in follicular fluid (FF) on early in vitro fertilization (IVF) outcomes remains unexplored. This study investigated the associations between OPFR metabolite (mOPFR) concentrations in FF and early IVF outcomes among 155 infertile women. Multivariate linear regression revealed negative associations between the concentrations of total mOPFRs in FF with the number of oocytes retrieved ($\beta = -0.63$, 95 % CI: −1.01 to −0.25, $p = 0.001$), between bis(1,3-dichloro-2-propyl) phosphate (BDCIPP) with the number of oocytes retrieved ($\beta = -0.84$, 95 % CI: −1.47 to −0.21, $p = 0.009$), and between bis(2-chloroethyl) phosphate (DBP) with the rate of high-quality day-3 embryos ($\beta = -6.01$, 95 % CI: −11.54 to −0.48, $p = 0.033$). The Bayesian kernel machine regression (BKMR) model identified BDCIPP as the dominant risk factor (posterior inclusion probability = 0.97) among five mOPFRs, corroborating the result of weighted quantile sum (WQS) models. Our findings revealed that BDCIPP in FF is a critical risk factor for the reduced number of oocytes retrieved, emphasizing that further research should focus on BDCIPP when exploring the effects of OPFR exposure on pregnancy outcomes. This study indicated that targeted policies and safe reproductive health strategies are warranted.

## 1. Introduction

The total number of infertile couples worldwide is estimated at 186 million people (Qiao et al., 2021), with projections indicating an increase of 2.5 times every 5 years to 2.5 times every 2 years (Qiao et al., 2014). In addition to the negative influence of delaying marriage and childbearing in women of reproductive age on couple fecundability (Nelson et al., 2013; Qiao et al., 2014), environmental influences on reproduction are under increasing scrutiny (Skakkebæk et al., 2022). Ecological data showed that sperm concentration and total sperm count declined by 51.6 % and 62.3 %, respectively, in industrialized countries, corelating with the proliferation of persistent organic pollutants after World War II (Carlsen et al., 1992; Levine et al., 2023). A large number of prospective cohort studies have indicated that many

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endocrine-disrupting chemicals (EDCs), such as persistent organic pollutants, organophosphate esters, and bisphenol A, adversely affect human ovarian functions, successful implantation, and clinical pregnancy (Buck Louis et al., 2013; Hu et al., 2020; Lin et al., 2021; Peters et al., 2024).

Organophosphorus flame retardants (OPFRs) are one of the most widely used EDCs as flame retardants, plasticizers, and antifoaming agents in various commercial products; as such, these chemicals have high detection frequency and concentration in various environmental samples, such as air (Lai et al., 2015), surface water (Cristale et al., 2013), and indoor dust (Tan et al., 2018). OPFRs and their metabolites have been detected in human urine, serum, and even breast milk from various regions, with detection frequencies reaching 70–100 % (Carignan et al., 2017; Varshavsky et al., 2021; Zhao et al., 2022; Liu et al., 2023; Kim et al., 2014). Thus, the endocrine-disrupting effects of OPFR metabolites (mOPFRs) have garnered significant scientific and public attention.

In vitro assays indicated that OPFRs are gonadal hormone disruptors, and their related mechanisms are complex and remain unknown (Ji et al., 2020). Animal studies showed that exposure to OPFRs and their metabolites disrupts thyroid hormones (Farhat et al., 2013), disturbs the hypothalamus–pituitary–gonad axis (Wang et al., 2015; Zhang et al., 2020), results in ovarian retardation (Li et al., 2019), and leads to impaired female reproduction. Carignan et al. (2017) conducted the first epidemiologic study to investigate the impact of mOPFRs exposure on fertility among women receiving in vitro fertilization (IVF). They found that the concentrations of maternal urinary mOPFRs were negatively associated with the successful fertilization rate, embryo implantation rate, clinical pregnancy rate, and live birth rate (Carignan et al., 2017). They also detected the same mOPFRs in the urine sample of the male partners and reported that paternal urinary mOPFRs were not associated with all the pregnancy outcomes, except for bis(1,3-dichloro-2-propyl) phosphate (BDCIPP), which was associated with reduced fertilization (Carignan et al., 2018). In general, OPFRs are considered to metabolize quickly in human bodies, so the concentrations of urinary mOPFRs may fluctuate although they had adjusted the urinary concentrations with specific gravity, which might increase the risk of bias in the results.

This study is the first to detect mOPFR concentrations in follicular fluid (FF) and explore the associations between these mOPFR concentrations in FF and the developmental outcomes of oocytes and embryos among infertile women undergoing IVF treatment.

## 2. Materials and methods

### 2.1. Study population

This prospective study was carried out in the Reproductive Medicine Center of the Eighth Affiliated Hospital of Southern Medical University (The First People's Hospital of Shunde). Patients under 40 years old who underwent IVF treatment from June 2021 to December 2022 were screened. All participants resided in the Shunde state for at least 1 year. The exclusion criteria were as follows: i. participants with diminished ovarian reserve, characterized by antral follicle count (AFC) $<$ 5–7 or anti-Mullerian hormone (AMH) $<$ 1.1 ng/mL; ii. history of $\geq$ 2 prior oocyte retrievals (ORs); iii. cycle cancellation; and iv. recurrent spontaneous abortion or adverse pregnancy histories. Only one IVF cycle was included for each participant.

This study was approved by the ethical committee of the Eighth Affiliated Hospital, Southern Medical University (20210301). Patients recruited agreed to participate and signed the informed consent form.

### 2.2. Clinical data and IVF outcomes

All participants completed a uniform questionnaire about age, race, occupation, smoking history, common environmental pollutant exposure, medication history, and other socio-demographic information, which were reviewed at consultation.

Assisted reproductive technology procedures, including ovarian stimulation, oocyte retrieval, insemination, and embryo freezing, were conducted according to the standard procedures. Standard ovarian stimulation with gonadotrophin (Gn) was performed using either a gonadotrophin-releasing hormone (GnRH) antagonist protocol or a long GnRH agonist protocol. Oocyte retrieval was performed 35–37 h after triggering with human chorionic gonadotropin (HCG), a GnRH agonist, or combined HCG and GnRH agonist under transvaginal ultrasound guidance. Oocytes were fertilized by conventional IVF. Successful fertilization was confirmed by the presence of two pronuclei at 16–18 h after conventional IVF. The fertilization number refers to the total number of inseminated. The successful fertilization rate was calculated by dividing the number of successful fertilizations by the total number of fertilizations. Embryos with at least four cells and $<$ 30 % fragmentation were considered viable embryos. High-quality embryos were defined as those with 7–9 cells of equal size, regular shape, and $<$ 10 % fragmentation. Fresh cycle treatment characteristics and outcomes were collected from electronic records of fertility clinics and hospitals. The rate of high-quality day-3 embryos was calculated as the number of high-quality day-3 embryos divided by the successful fertilization number.

Participants underwent routine gonadal steroid hormone measurement during ovarian stimulation. From each patient, FF was gently aspirated from the first three large follicles (diameter $>$14 mm) at the time of oocyte retrieval and mixed together. Flushing with medium was omitted during aspiration. Only FF samples without obvious blood contamination were retained for further analyses. Each FF sample was centrifuged at 716 *g* for 10 min, and the supernatant was collected and stored at −80 °C for subsequent analysis.

This study conducted all hormonal measurements in the Department of Clinical Laboratory of the Eighth Affiliated Hospital of Southern Medical University (The First People's Hospital of Shunde). Automated chemiluminescent immunoassay kits (DxI 800 Access Immunoassay System, Beckman Coulter Inc., USA) were used to measure the levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, prolactin (PRL), and testosterone. AMH was measured using a chemiluminescent immunoassay diagnostic kit (Guangzhou Kangrun Biotech Co., Ltd., China). The total coefficient of variation was $<$ 10 %.

### 2.3. Measurement of mOPFRs in FF samples

Internal standards were added into 2 mL of FF (10 ng/mL for each standard compound). The pH was adjusted to 3 by adding 12 μL of formic acid. The 60 mg WAX cartridges (CNW, Shanghai, China) were pre-washed with 2 mL of methanol solution containing 5 % $NH_4OH$ and 3 mL of an aqueous solution with 0.6 % formic acid. After sample loading, 2 mL of 30 % methanol in water solution was employed to eliminate interferences. Target analytes were eluted using 2 mL of 5 % $NH_4OH$ in methanol. The eluate was collected and evaporated to dryness, and the residue was re-dissolved in 200 μL of a 40 % methanol solution. The extracts were then stored at −20 °C until further analysis. All target compounds were separated by a CAPCELL PAK C18 column (100 mm × 3 mm, 3 μm particle diameter, Agilent) and determined by high-performance liquid chromatography–triple quadrupole mass spectrometry (HPLC-QQQ-MS/MS). mOPFRs were analyzed by applying a gradient of 10 mM ammonium acetate (A) and methanol (B). The gradient of the mobile phase was as follows: 0–2 min, 5 %–15 % B, 2–2.1 min, 15 %–50 % B, 2.1–10 min, 50 % B; 10–11 min, 50 %–90 % B; 11–12 min, 90 % B; 12–13 min, 90 %–99 % B; 13–14 min, 99 % B; and 14–15 min, 99 %–5 % B. The flow was 0.2 mL/min, and the column temperature was maintained at 35 °C. The MS conditions were as follows: negative ESI, gas temperature of 325 °C, gas flow of 5 L/min, nebulizer pressure of 45 psi, capillary voltage of 3500 V, and dwell time of 30 ms.

Every batch of samples incorporated one procedural blank, one reagent blank, and one matrix spike to ensure the precision of the analysis outcome. The samples were used to assess the recoveries and background contaminations of the target compounds during the pretreatment stage. The recovery efficiencies of the mOPFR congeners ranged from 84 % to 114 %. The calibration curves were in the range of 0.01–100 μg/L, and the correlation coefficients exceeded 0.993.

### 2.4. Statistical analysis

The basic characteristics of 155 participants in the study were described by mean values ± standard deviation (SD) and percentages. Low limit of detection (LLOD), detection frequency (%), and mean ± SD were adapted to describe the distribution of mOPFR concentrations in FF. The mOPFR concentrations in FF, which were below the LLOD, were calculated as LLOD/$\sqrt{2}$ (Carignan et al., 2017, Hu et al., 2020).

The multivariate linear regression model was employed to analyze the associations between mOPFR concentrations in FF and IVF outcomes, as well as the E2 level in serum on the HCG trigger day among infertile women. We adjusted for women's age at oocyte pick-up (OPU), body mass index (BMI), infertility duration, AMH concentration, number of AFC, and total Gn dosage. The full model equation is as follows: $Y = \beta_0 + \beta_1$((bis(2-butoxyethyl) phosphate (BBOEP)) + $\beta_2$(bis(2-chloroethyl) phosphate (BCEP)) + $\beta_3$(BDCIPP) + $\beta_4$(dibutyl phthalate (DBP)) + $\beta_5$(diphenyl phosphate (DPHP)) + $\beta_6$(age) + $\beta_7$(BMI) + $\beta_8$(infertility duration) + $\beta_9$(AMH concentration) + $\beta_{10}$(number of AFC) + $\beta_{11}$(total Gn dosage) + $\varepsilon$. "$\varepsilon$" of the model denotes the random error term, representing residual variability unaccounted for by the model predictors. The coefficients estimated by the multivariate linear regression model were reported as $\beta$ values and their 95 % confidence intervals (95 % CIs). A $p$-value $< 0.05$ was reported to be statistically significant.

A novel strategy, namely, Bayesian kernel machine regression (BKMR), was employed to evaluate complex environmental contaminants to explain possible non-linearity and interactions among exposures (Bobb et al., 2015; Valeri et al., 2017). We used the BKMR model, which was proposed by Bobb et al. (2015), to evaluate the joint effects of mOPFR concentrations in FF and IVF outcomes. We modeled the IVF outcomes as a smooth function by using a Gaussian kernel function to identify nonlinear and non-additive relationships between mOPFR concentrations in FF and IVF outcomes. We developed the BKMR model as follows: Yi = h (BBOEP, BCEP, BDCIPP, DBP, DPHP) + $\beta^{T}$Zi + ei. The function of h () represents a dose–response relationship and contains nonlinear and/or interactions between each component, with Z = Z1, …, Zp as p potential confounders (confounders are consistent with the multivariate linear regression model) (Valeri et al., 2017). Considering the strong correlation of mOPFR concentrations in our analysis, we conducted a variable selection method with 1000 iterations of a Markov chain Monte Carlo algorithm. Summary statistics were derived from the model fit to quantify relevant features of the exposure–response function, thereby elucidating the cumulative effects of the mixture.

The BKMR model showed many cross-sectional views of the surface. Specifically, we plotted the cumulative effects of mOPFR concentrations in FF by comparing the estimated value of the exposure–response function while fixing all other exposures constant at a particular quantile. We also summarized the single-exposure effects of each concentration of mOPFRs in FF, and all other mOPFR concentrations in FF were positioned at certain quantiles. In addition, we plotted a dose–response relationship of each concentration of mOPFR in FF with IVF outcomes among infertile women, and the concentrations of the remaining mOPFRs in FF were fixed at their 50th percentile. Posterior inclusion probability (PIP) was calculated to represent the different contributions of each concentration of mOPFR in FF to IVF outcomes among infertile women. The widely used PIP threshold is 0.5 to determine whether the factor is important (Coker et al., 2018). A high PIP value indicates a substantial influence of the individual mOPFR on IVF outcomes. Finally, the interactions between pairs of chemicals were examined while maintaining other mOPFR concentrations in FF at their 50th percentile exposure levels (Chiu et al., 2018).

The weighted quantile sum (WQS) model was applied to validate the results of the BKMR model and identify the main contributors to assess the contribution of individual mixture components (Carrico et al., 2015). This approach incorporated five mOPFR concentrations in FF, ensuring they demonstrated a consistent directional effect on IVF outcomes. The WQS regression model created a weighted linear index that represented the body burden of the five mOPFR concentrations. In each WQS model, weights were employed to identify the primary factors influencing IVF outcomes among infertile women. The full model equation is as follows: WQS index = $w_1$ * $q$(BBOEP) + $w_2$ * $q$(BCEP) + $w_3$ * $q$(BDCIPP) + $w_4$ * $q$(DBP) + $w_5$ * $q$(DPHP). "$w$" of the model refers to weight, which quantifies the relative contributions of each mOPFR to the mixture effect. The confounders were aligned with the multivariate linear regression model.

The multivariate linear regression model was carried out using SPSS v25.0 (SPSS Inc., Chicago, IL, USA). BKMR (bkmr package) was performed using R package "bkmr" (R version 4.4.2), and the quantifiable and visualized results of the BKMR model were plotted using the "ggplot" program. The WQS model was fitted by the R package "gWQS" (R version 4.4.2).

## 3. Results

### 3.1. Study population characteristics

The demographic and baseline characteristics of the 155 participants are summarized in Table 1 ($n = 155$). The female's average age at OPU was 31.67 ± 3.71 years, the mean concentration of AMH was 4.90 ± 0.29 ng/mL, and the average number of AFC was 13.00 ± 2.08. A total of 84 women (53.85 %) of the study population were diagnosed with primary infertility, and 72 women (46.15 %) were diagnosed with secondary infertility at the time of enrollment. The clinical characteristics of infertile female are presented in Table S1. The mean E2 level in serum on HCG trigger day was 3661.79 ± 3762.05 pg/mL, the mean number of oocytes retrieved was 10.20 ± 0.58, the mean successful fertilization rate was 64.38 %±2.18 %, the mean number of high-quality day-3 embryos was 2.33 ± 0.67, and the mean rate of high-quality day-3

**Table 1**
Demographic characteristics of the participants (n = 155).

| Characteristics | Mean ±SD or n (%) |
|---|---|
| Age of oocytes retrieval (years) | 32.75 ± 5.68 |
| BMI ( kg/m2 ) | 22.26 ± 2.42 |
| Duration of infertility (years) | 4 ± 4.08 |
| Rate of primary infertility | 83 (53.55 %) |
| Rate of secondary infertility | 72 (46.45 %) |
| Infertility factors | |
| Female pelvic and fallopian tube factors | 82 (52.90 %) |
| Ovulation disorders | 3 (1.94 %) |
| Endometriosis | 8 (5.16 %) |
| Couple factors | 33 (21.29 %) |
| Male factors | 19 (12.26 %) |
| Other factors | 10 (6.45 %) |
| Basal sex hormone levels | |
| FSH level (IU/L) | 6.06 ± 1.43 |
| LH level (IU/L) | 4.74 ± 0.50 |
| E2 level (pg/mL) | 39.78 ± 27.45 |
| P level (ng/mL) | 0.64 ± 0.25 |
| T level (nmol/L) | 2.13 ± 1.04 |
| PRL level (ng/mL) | 12.80 ± 5.94 |
| AMH level (ng/mL) | 5.27 ± 2.60 |
| Number of AFC | 12.50 ± 3.11 |

Note: AFC, Antral follicle counting; AMH, Anti-mullerian hormone; BMI, Body mass index; E2, Estradiol; FSH, Follicle-stimulating hormone; LH, Luteinizing hormone; P, Progesterone; PRL, Prolactin; SD, Standard deviation; T, Testosterone.

embryos was 54.04 %±2.75 %.

### 3.2. Detection frequency and mOPFR concentrations in FF

The detection frequency and concentrations of all mOPFRs in FF are shown in Table 2. Detection frequencies were high for BBOEP (74.84 %), BDCIPP (69.68 %), DBP (67.74 %), and BCEP (66.45 %) but low for DPHP (55.48 %). The highest mean concentration of individual mOPFRs was 0.54 ± 1.44 ng/mL for BDCIPP in FF, followed by DBP with 0.46 ± 0.90 ng/mL, whereas BBOEP had the lowest mean concentration at 0.03 ± 0.05 ng/mL. All concentrations of the target chemicals presented a right-skewed distribution.

### 3.3. Associations between mOPFRs in FF and IVF outcomes among infertile women analyzed by the multivariate linear regression model

The multivariate linear regression model was used to analyze the correlations between mOPFR concentrations and IVF outcomes (Table 3). The concentration of BDCIPP in FF was negatively associated with the number of oocytes retrieved ($\beta = -0.84$, 95 % CI: −1.47 to −0.21, $p = 0.009$). The rate of high-quality day-3 embryos decreased with increasing concentration of DBP in FF ($\beta = -6.01$, 95 % CI: −11.54 to −0.48, $p = 0.033$). Moreover, the concentrations of total mOPFRs in FF were negatively associated with the number of oocytes retrieved ($\beta = -0.63$, 95 % CI: −1.01 to −0.25, $p = 0.001$).

### 3.4. Associations between mOPFR concentrations in FF and IVF outcomes among infertile women assessed by the BKMR model

The BKMR model was used to further investigate the relationships between mOPFR concentrations in FF and IVF outcomes among infertile women. A positive tendency was observed between mOPFRs and E2 level in serum on the HCG trigger day (Fig. 1a). Moreover, a negative tendency was detected between mOPFRs and the number of oocytes retrieved (Fig. 1b). However, these tendencies were not statistically significant. With the concentrations of other mOPFRs fixed at their 50th exposure levels, the concentration of BDCIPP in FF showed a negative correlation with the number of oocytes retrieved and the rate of high-quality day-3 embryos (Figs. S2b and S2d); these tendencies also were not statistically significant (Fig. S1). In addition, we calculated PIPs under the BKMR model (Table 4). BDCIPP made the greatest contribution among the effects of mOPFRs in FF on the E2 level in serum on the HCG trigger day (PIP=0.58) and the number of oocytes retrieved (PIP=0.97). In the analysis of the successful fertilization rate, BDCIPP, BCEP, and DBP in FF had high PIPs of 0.21, 0.18, and 0.11, respectively (Table 4).

In analyses assessing the effects of exposure to five mOPFRs on the E2 level in serum on HCG trigger day, the number of oocytes retrieved, the successful fertilization rate, and the rate of high-quality day-3 embryos, several mOPFRs showed potential interactions in vivo (e.g., BDCIPP with DBP, BDCIPP with BBOEP, and BBOEP with DBP; Fig. S3). However, bivariate exposure−response function analyses indicated that none of these interactions reached statistical significance (all interaction $p$-values >0.05).

**Table 3**
Multivariable linear analysis of the association between the mOPFR concentrations in FF and the following outcomes (n = 155).

| Outcomes | mOPFRs | β (95 %CI) | p-value |
|---|---|---|---|
| E2 level in serum on HCG trigger day | BCEP | −10.96 (−978.75, 956.83) | 0.982 |
| | DPHP | −177.07 (−549.99, 195.85) | 0.350 |
| | DBP | −55.70 (−463.86, 352.46) | 0.788 |
| | BDCIPP | −57.98 (−309.81, 193.85) | 0.650 |
| | BBOEP | 671.47 (−6860.95, 8203.89) | 0.860 |
| | ΣmOPFRs | −84.44 (−234.91, 66.04) | 0.269 |
| Number of oocytes retrieved | BCEP | −1.77 (−4.20, 0.65) | 0.151 |
| | DPHP | −0.07 (−1.00, 0.85) | 0.874 |
| | DBP | −0.46 (−1.48, 0.57) | 0.380 |
| | BDCIPP | −0.84 (−1.47, 0.21) | **0.009** |
| | BBOEP | −12.07 (−30.95, 6.81) | 0.209 |
| | ΣmOPFRs | −0.63 (−1.01, −0.25) | **0.001** |
| Successful fertilization rate | BCEP | −4.27 (−14.83, 6.29) | 0.426 |
| | DPHP | 1.02 (−2.97, 5.02) | 0.613 |
| | DBP | −2.72 (−7.14, 1.70) | 0.226 |
| | BDCIPP | 2.51 (−0.21, 5.24) | 0.070 |
| | BBOEP | 15.22 (−66.12, 96.56) | 0.712 |
| | ΣmOPFRs | 0.54 (−1.14, 2.22) | 0.526 |
| Rate of high-quality day−3 embryos | BCEP | −1.97 (−15.18, 11.24) | 0.768 |
| | DPHP | 4.17 (−0.83, 9.17) | 0.101 |
| | DBP | −6.01 (−11.54, −0.48) | **0.033** |
| | BDCIPP | −0.17 (−3.58, 3.24) | 0.922 |
| | BBOEP | 56.37 (−45.38, 158.12) | 0.275 |
| | ΣmOPFRs | −2.38 (−2.34, 1.86) | 0.823 |

Note: ΣmOPFRs, the total concentration of mOPFRs; CI, Confidence interval; E2, Estradiol; HCG, Human chorionic gonadotropin; mOPFRs, Organophosphorus flame retardant metabolites; β, Regression coefficient. Models were adjusted for the average age at oocyte pick-up (OPU), BMI, the duration of infertility, the concentration of AMH, the number of AFC, total Gn dosage.

### 3.5. Associations between mOPFRs in FF and IVF outcomes among infertile women assessed by the WQS regression model

The WQS regression model showed that BDCIPP, BCEP, and DBP had high weights among the effects of five mOPFRs in FF on the E2 level in serum on the HCG trigger day (weight=0.74, 0.12, and 0.05, respectively) and the number of oocytes retrieved (weight=0.49, 0.27, and 0.13, respectively) (Figs. 2a and b and Table S2). The weights of BDCIPP, DBP, and DPHP were 0.68, 0.19, and 0.08, respectively, indicating a significant effect on the successful fertilization rate (Fig. 2c and Table S2).

## 4. Discussion

This study is the first to explore the associations between the mOPFR concentrations in FF and IVF outcomes among infertile women. In this prospective study, multivariate linear regression revealed negative associations between the concentrations of total mOPFRs and BDCIPP in FF with the number of oocytes retrieved. Moreover, the BKMR and WQS

**Table 2**
Distribution of the mOPFR concentrations in FF (n = 155).

| mOPFRs (ng/mL) | LLOD ($\times 10^{-3}$) | DF (%) | Mean ±SD (ng/mL) | Percentiles | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | 5th | 25th | 50th | 75th | 95th |
| **BCEP** | 10.30 | 66.45 | 0.19 ± 0.39 | 0.01 | 0.01 | 0.04 | 0.25 | 0.84 |
| **DPHP** | 0.67 | 55.48 | 0.40 ± 1.05 | 0.00 | 0.00 | 0.00 | 0.25 | 2.30 |
| **DBP** | 1.01 | 67.74 | 0.46 ± 0.90 | 0.00 | 0.00 | 0.13 | 0.46 | 2.43 |
| **BDCIPP** | 5.39 | 69.68 | 0.54 ± 1.44 | 0.00 | 0.00 | 0.06 | 0.34 | 2.54 |
| **BBOEP** | 0.01 | 74.84 | 0.03 ± 0.05 | 0.00 | 0.00 | 0.01 | 0.05 | 0.16 |

Note: DF, Detection frequency; FF, Follicular fluid; LLOD, Lower limit of detection; mOPFRs, Organophosphorus flame retardant metabolites; SD, Standard deviation.

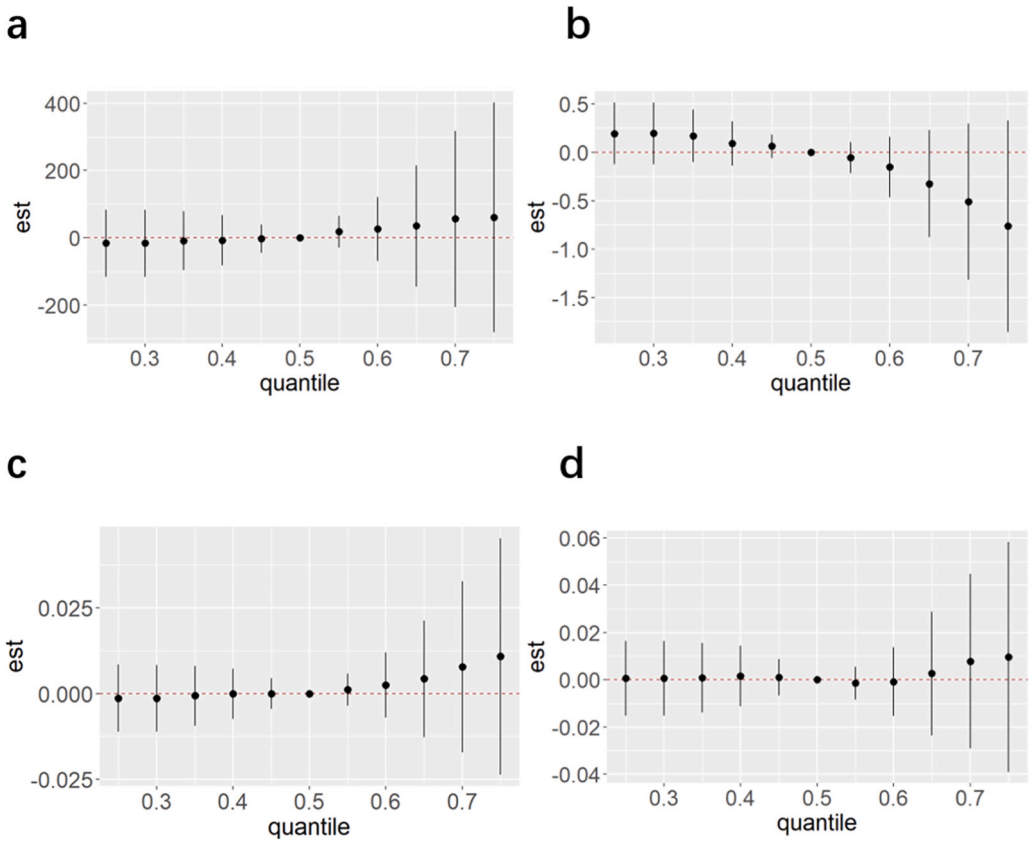


**Fig. 1.** The overall risk (95 %CI) of the mixture of concentrations of mOPFRs in FF on (a) the E2 level in serum on HCG trigger day, (b) the number of oocytes retrieved, (c) the successful fertilization rate and (d) the rate of high-quality day-3 embryos in BKMR model, when all chemicals were compared at different percentiles with their 50th percentiles. est represented exposure-outcome relationships. Models were adjusted for the average age at oocyte pick-up (OPU), BMI, the duration of infertility, the concentration of AMH, the number of AFC, total Gn dosage.

**Table 4**
PIPs derived from the BKMR model into the E2 level in serum on HCG trigger day, the number of oocytes retrieved, the successful fertilization rate and the rate of high-quality day-3 embryos.

| Variable | PIPs | | | |
|---|---|---|---|---|
| | E2 level in serum on HCG trigger day | Number of oocytes retrieved | Successful fertilization rate | Rate of high-quality day-3 embryos |
| **BDCIPP** | 0.58 | 0.97 | 0.21 | 0.29 |
| **BCEP** | 0.10 | 0.55 | 0.18 | 0.20 |
| **DBP** | 0.07 | 0.27 | 0.11 | 0.50 |
| **BBOEP** | 0.08 | 0.22 | 0.02 | 0.30 |
| **DPHP** | 0.18 | 0.12 | 0.06 | 0.40 |

Note: PIP: Posterior inclusion probability. Models were adjusted for the average age at oocyte pick-up (OPU), BMI, the duration of infertility, the concentration of AMH, the number of AFC, total Gn dosage.

models identified BDCIPP as the primary risk contributor among the five detected mOPFRs.

The detection frequencies of mOPFRs in FF fluctuated from 55.48 % to 74.84 %, which were slightly lower than those in serum (70 %–100 %) (Liu et al., 2023) and urine (80 %–90 %) (Varshavsky et al., 2021; Zhao et al., 2022). FF is formed from the bloodstream of the ovarian cortex and the components secreted by the cell layers within the follicle (Hennet and Combelles, 2012; Rodgers and Irving-Rodgers, 2010). Therefore, the detection frequencies and mOPFR concentrations in FF were lower than those in peripheral blood circulation. Among the five mOPFRs, the mean concentration and detection frequency were the highest for BDCIPP (0.54 ± 1.44 ng/mL and 69.68 %, respectively). Other studies reported that BDCIPP has a high detection frequency and concentration among all the detected mOPFRs in urine (He et al., 2018; Zhao et al., 2022). The present results suggested that BDCIPP may significantly influence fertility.

Our study found a negative correlation between the concentration of BDCIPP in FF and the number of oocytes retrieved, as determined by a multivariate linear regression model. The BKMR and WQS models revealed that BDCIPP was the main risk factor among the five mOPFRs. Carignan reported that the paternal urinary levels of BDCIPP were negatively associated with the probability of fertilization in 201 couples undergoing IVF treatment (Carignan et al., 2018). Another case–control study reported that the concentration of maternal urinary BDCIPP is associated with fetal chromosome abnormality (Shahin et al., 2024). In vivo studies have demonstrated that mOPFRs can cause fetal DNA damage and chromosomal abnormalities because of the accumulation of reactive oxygen species (Duhig et al., 2016; Ingle et al., 2020). Moreover, Hoffman et al. (2018) reported that BDCIPP exposure is associated with preterm birth in females. All the above studies were consistent with our findings that BDCIPP had detrimental effects on early pregnancy outcomes. Other mOPFRs also had adverse effects on pregnancy outcomes, such as spontaneous abortion (Zhao et al., 2021), clinical pregnancy (Carignan et al., 2017), fetal birthweight, and fetal birth length (Luo et al., 2021). Therefore, further investigations should be conducted to prevent the exposure of women of reproductive age to OPFRs, and environment-friendly products should be developed to protect human reproductive health.

Experimental evidence of mOPFR-induced alterations of reproductive hormones may elucidate our findings. A previous animal experiment showed that BDCIPP interferes with estrogen synthesis in zebrafish by playing an agonistic effect on estrogenic receptor alpha and

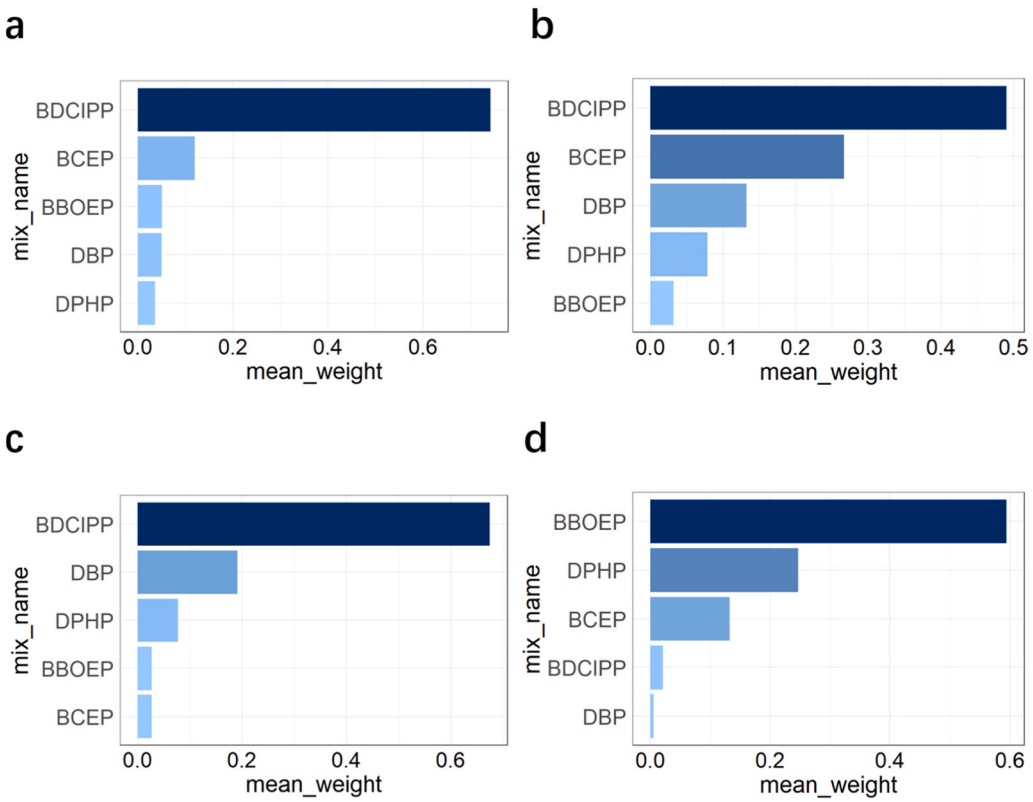


**Fig. 2.** WQS model regression index weights for (a) the E2 level in serum on HCG trigger day, (b) the number of oocytes retrieved, (c) the successful fertilization rate and (d) the rate of high-quality day-3 embryos. Models were adjusted for the average age at oocyte pick-up (OPU), BMI, the duration of infertility, the concentration of AMH, the number of AFC, total Gn dosage.

upregulating the genes of 17$\beta$HSD and CYP19 in H295R cells, which encode enzymes involved in estrogen synthesis (Zhang et al., 2020). Moreover, BDCIPP disrupted progesterone synthesis by inhibiting the genes of CYP11A1, STAR, and 3-$\beta$HSD (Zhang et al., 2020). We speculated that the disturbance of estrogen and progesterone interrupted the hypothalamic–pituitary–gonadal axis (Zhang et al., 2020) and affected follicle development and ovulation. In addition, BDCIPP increased the conversion of androstenedione into testosterone by upregulating CYP17 (Zhang et al., 2020). The high level of testosterone increased follicular atresia but inhibited the FSH-induced proliferation of granulosa cells (Liu et al., 2015), thereby affecting follicle recruitment and ovulation. This study further showed that exposure to BDCIPP led to increased mortality and decreased hatchability in zebrafish embryos (Zhang et al., 2020). Accordingly, we speculated that BDCIPP affected follicle development and ovulation by interfering with reproductive hormone levels, resulting in reduced numbers of oocytes retrieved. However, our study did not find a statistically significant effect of BDCIPP exposure on serum E2 level on the HCG trigger day. The E2 level was measured in serum rather than in FF, whereas the levels of mOPFRs were detected in FF. In this regard, we did not observe the association between the BDCIPP concentration in FF and serum E2 level on the HCG trigger day.

Previous studies also demonstrated that exposure to OPFRs, which metabolize to mOPFRs in vivo (Shahin et al., 2024), changed the transcriptome (Wang et al., 2023b), cell phenotypes (Wang et al., 2022), and steroidogenic function (Wang et al., 2023a) of KGN human ovarian granulosa cells, thereby affecting the structure and function of granulosa cells (Wang et al., 2022, 2023a, 2023b). The destruction of ovarian granulosa cells would result in follicular atresia and oocyte degeneration (Yeung et al., 2017) because granulosa cells play critical roles in ovarian physiology and oocyte development. Therefore, we speculated that mOPFRs contribute to the decreased number of oocytes retrieved, potentially by disrupting sex hormone levels and destroying ovarian granulosa cells.

The advantage of this study is that we directly collected FF to determine the mOPFR concentrations. We adopted novel BKMR and WQS models to analyze the relationship between mOPFRs in FF and early IVF outcomes. Moreover, the subjects of our study were all infertile women with normal ovarian reserve who underwent IVF treatment, allowing for an early and precise assessment of the effects of mOPFR concentrations in FF on human fecundity, as evidenced by fertilization and embryo development outcomes. However, our research had some limitations. First, we only followed up early IVF outcomes but did not monitor further clinical pregnancy outcomes. Second, BKMR demonstrated negative correlations between the concentrations of total mOPFRs and BDCIPP in FF and the number of oocytes retrieved. However, these associations did not reach statistical significance, potentially due to insufficient statistical power resulting from the limited sample size. Thus, multi-site and large-sample studies are ideal to elucidate the complex effects of exposure to OPFRs on human reproductive health in the future.

## 5. Conclusion

The concentration of BDCIPP in FF was negatively associated with the number of oocytes retrieved in infertile women undergoing IVF, and BDCIPP emerged as the major risk factor among the five detected mOPFRs. These results provide epidemiological evidence for the toxic effect of BDCIPP on human fecundity. Future studies should focus on BDCIPP when exploring the effects of mOPFR concentrations in FF on human reproductive health. Moreover, this study provides a theoretical foundation for promoting the revision of international policies and guidelines concerning exposure to OPFRs and mOPFRs.

## CRediT authorship contribution statement

**Zenghua Qi:** Validation, Project administration, Methodology, Investigation, Conceptualization. **Chaoyang Long:** Methodology, Investigation, Data curation, Conceptualization. **Jie Yang:** Validation, Software, Methodology, Conceptualization. **Xuelan Li:** Writing – review & editing, Writing – original draft, Project administration, Investigation, Formal analysis, Conceptualization. **Xianli Zhou:** Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation. **Yingxin Yu:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Xin Chen:** Writing – review & editing, Visualization, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization. **Jinying Xie:** Visualization, Software, Methodology, Data curation. **Min Lin:** Software, Formal analysis, Data curation, Conceptualization. **Yaqi Cao:** Software, Methodology, Data curation. **Xinyu Dou:** Validation, Investigation, Data curation.

## Ethics approval consent to participate

The approval for this study was obtained from the ethical committee of the Eighth Affiliated Hospital, Southern Medical University (20210301). And patients recruited in this study have all agreed to participate and signed informed consent form.

## Consent for publication

Written informed consent for publication was obtained from the patients.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2025.119218.

## Data availability

Data will be made available on request.

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