Environmental Pollution 359 (2024) 124474

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

Exposure of women undergoing in-vitro fertilization to per-and polyfluoroalkyl substances: Evidence on negative effects on fertilization and high-quality embryos

Juan Shen [a,1], Yuchan Mao [f,1], Hongyan Zhang [b], Hangying Lou [a], Ling Zhang [a], Joaquim Paulo Moreira [c,d,e,2,*], Fan Jin [a,2,**]

[a] Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, China
[b] Hangzhou Women's Hospital, 369 Kunpeng Road, Hangzhou, China
[c] International Healthcare Management Research and Development Center (IHM_RDC), The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Shandong, Jinan, China
[d] Henan Normal University, School of Social Affairs, Xinxiang, China
[e] Atlantica Instituto Universitario, Gestao em Saude, Oeiras, Portugal
[f] Center for Reproductive Medicine, Department of Reproductive Endocrinology, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou, Zhejiang, China

ARTICLE INFO

Keywords:
Environmental exposure
Female reproductive health
IVF
PFAS mixtures
Public health
Infertility

ABSTRACT

In April 2023, the World Health Organization (WHO) reported that 17.5% of the global adult population experience infertility. What may be the contribution of per-and polyfluoroalkyl (PFAS) to this global public health problem?

This study explored the associations between in vitro fertilization (IVF) outcomes and plasma concentrations of individual PFAS and PFAS mixtures in women undergoing in vitro fertilization and embryo transfer (IVF-ET) and how these exposures might affect IVF outcomes. We analyzed 8 PFASs in plasma samples from women (N = 259) who underwent IVF treatment. In multivariable generalized linear mixed models, there were statistically significant associations of higher plasma concentrations of PFNA with reduced numbers of total retrieved oocytes [12.486 (95%CI: 0.446,25.418), p trend = 0.017], 2 PN zygotes [6.467(95%CI: 2.034,14.968), p trend = 0.007], and cleavage embryos [6.039(95%CI: 2.162,14.240), p trend = 0.008]. Similarly, there was a continuous decline in the numbers of retrieved 2 PN zygotes and cleavage embryos with increasing concentration of PFOS [6.467 (95%CI: 2.034,14.968), p trend = 0.009 and 6.039(95%CI: 2.162,14.240), p trend = 0.031,respectively] and a negative association between PFHxS concentrations and clinical pregnancy during the initial cycles of frozen ET [0.525(95%CI:0.410,0.640), p trend = 0.021]. To investigate the joint effect of PFAS mixtures, a confounder-adjusted BKMR model analysis showed inverse relationship between PFAS mixtures and the number of high-quality embryos, 2 PN zygotes and cleavage embryos, to which the greatest contributors to the mixture effect are PFDeA and PFBS, respectively. It demonstrated that PFAS exposure might exert negative effects on oocyte yield, fertilization and high-quality embryo in women undergoing IVF. These findings suggest that exposure to PFAS may increase the risk of female infertility and further studies are needed to uncover the potential mechanisms underlying the reproductive effects associated with PFAS.

* co-Corresponding author. The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Shandong, Jining Road, 20445, Jinan, Shandong, China.
** co-Corresponding author. Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, China.
E-mail addresses: jpm2030@outlook.com, paulo.moreira@sd-hospital.cn (J.P. Moreira), jinfan1@zju.edu.cn (F. Jin).
[1] Co-First Authors: Juan Shen and Yuchan Mao.
[2] **Joaquim Paulo Moreira** and **Fan Jin** are co-Corresponding authors.

https://doi.org/10.1016/j.envpol.2024.124474
Received 12 March 2024; Received in revised form 27 June 2024; Accepted 28 June 2024
Available online 9 July 2024

1. Background

Infertility is generally defined as the inability of a couple to develop pregnancy even after a year of unprotected frequent sexual intercourse. In April 2023, The World Health Organization (WHO) reported global data on infertility (WHO, 2023). The Western Pacific Region had the highest prevalence of lifetime infertility (23.2%), followed by the Region of the Americas (20.0%) and the European Region (16.5%) (WHO, 2023; Cox et al., 2022). In countries like China, the rate of female infertility among reproductive age has increased to a reported prevalence of about 25% (Zhou et al., 2018). There are several reasons for infertility, including advanced reproductive-age, unhealthy lifestyle, exposure to environmental toxins, and other issues(Swift et al., 2024; Presunto et al., 2023). Endocrine disruptors (EDCs) have been considered as one of the factors leading to infertility, impairing female fertility by altering the hormonal environment that plays an important role in the pathogenesis of infertility (Green et al., 2021).

Per-and polyfluorinated-alkyl substances (PFAS) are environmental endocrine-disrupting-chemicals (EDCs) and constitute a wide range of formulated compounds, characterized by carbon chains varying from 4 to 14 carbons in length adorned with multiple fluorine atoms (Giulivo et al., 2016; Marks et al., 2021; Padmanabhan et al., 2021). PFAS are recognized as problematic pollutants with adverse reproductive consequences, and these compounds have been widespread utilized in both market or commercial uses, including non-stick utensils foodstuffs, décor, carpets, cosmetics and along with different applications (Liu et al., 2018; Su et al., 2016; Sunderland et al., 2019). Human populations are frequently susceptible to PFAS exposure by inhalation, ingestion, and dermal exposure (Balk et al., 2019; Rice et al., 2020). PFAS are often found in urine, serum, follicular fluid, semen, umbilical cord blood and in infant milk, among other human biological specimens (Aro et al., 2021; Lamichhane et al., 2021; Zeng et al., 2023a). In the human body, PFAS exhibit limited elimination, characterized by half-lives that can extend to 5 years (Rosato et al., 2024). Various investigations in animal subjects have illustrated a range of toxic effects associated with PFAS, including impacts on reproduction, development, and neurological function (Lopez-Arellano et al., 2019; Wang et al., 2019a). As a result, two challenges arise. On the one hand, increase in public awareness about the probable threats posed by PFAS exposure to public health including blood-follicular transfer and associations with IVF-ET outcomes (Hong et al., 2022a) needs to be a major goal of scientific studies and evidence. On the other hand, practical solutions from stakeholders should be adopted. Especially considering that these chemicals are going to be present in the environment for many years to come, since, in the past, their use has been broadly uncontrolled.

Perfluorooctanoic acid (PFOA) may trigger oocyte apoptosis, necrosis, and corpus luteum dysfunction in pregnant mice through oxidative stress and apoptotic pathways (Lopez-Arellano et al., 2019; Chen et al., 2017). Additionally, perfluorobutane sulfonic acid (PFBS), perfluorononanoic acid (PFNA), and perfluorododecanoic acid (PFDoA) have been associated with ovarian dysfunction, health issues in female mice descendants and diminished levels of serum hormone levels (Zhang et al., 2021; Hjermitslev et al., 2020). In mice, prolonged intake of perfluorooctane sulfonic acid (PFOS) as been associated to impairing estrogen production, thus affecting the maturation of follicles and the process of ovulation (Feng et al., 2015). Observational research in humans indicate PFAS contact may result in delayed menarche, irregular menstrual cycles, early onset of menopause, early ovary dysfunction, and changes in the amounts of systemic sexual hormone level (Lopez-Espinosa et al., 2011; Zhou et al., 2017; Taylor et al., 2014; Zhang et al., 2018; Barrett et al., 2015). However, there have been few and limited studies into the potential pathways through which PFAS may impair human fertility in spite of recent evidence strengthening the need for further research (Rickard et al., 2022; Cohen et al., 2023; Xie et al., 2021).

Epidemiological research has revealed a link between women's exposure to PFAS and an increased likelihood of developing polycystic ovarian syndrome (PCOS), thus impairing women's sexuality (Di Nisio et al., 2020; Wang et al., 2019b). In participants conceiving in vitro fertilization (IVF), PFOA exhibited an inverse relation with fully developed oocytes, ZPN oocytes, and high-quality embryos (Ma et al., 2021). Conversely, a separate investigation had elaborated that PFAS in follicular-fluid exhibit no link with the rate of fertilization (Kim et al., 2020). Another review study indicated that no strong links between PFAS concentrations and IVF outcomes were observed in cross-sectional studies involving women undergoing IVF-ET (McCoy et al., 2017). Overall, previously published literature exploring the interrelationship between PFAS and women fertility has had very a scope and published evidence demonstrates inconsistency in published results.

As part of standard Assisted Reproductive Technology (ART) procedures, both the outcomes of treatment and collected samples present valuable prospects for exploring the connection between PFAS levels and in vitro fertilization (IVF) results, which may provide insights into the potential impact of PFAS on female reproductive health.

Additionally, we should note that people are exposed to various PFAS compounds. Unfortunately, most previous studies primarily examined individual PFAS and did not investigate the possible combined impact of PFAS mixtures on human reproductive capabilities. Precisely address this gap in knowledge and available evidence, this study aimed to assess the links between plasma levels of individual PFAS and PFAS mixtures in women undergoing IVF-ET and how these exposures might affect female IVF outcomes.

2. Materials and methods

2.1. Research participants

We focused on a cohort of 259 female volunteers recruited from couples receiving in vitro fertilization-embryo transfer (IVF-ET) procedures at a Chinese "Women's Hospital" from May 2017 to September 2018. The inclusion/exclusion criteria were defined to exclude as many other interfering factors as possible, including those that may affect the ovarian function and IVF outcomes, such as polycystic ovary syndrome, endometriosis, reproductive tract malformations, hereditary diseases, immunological factors, male non obstructive azoospermia and donor sperm or donor egg cycles. Male infertility only included males with obstructive azoospermia. Unexplained infertility refers to the absence of a clear cause of infertility, where the female ovaries and male sperm function normally. Women above the age of 40, as well as those with low ovulation retention (follicle-stimulating level of hormones greater than 12 mIU/mL or antral follicle counts less than five), were excluded. The Study follows the STROBE Protocol Statement's recommendations.

2.2. Collection of blood samples and PFAS measurement

Upon oocyte retrieval day, blood samples were obtained from female participants and collected in a sterile container with EDTA, amounting to approximately 1 mL in total. Following collection, the samples were subjected to centrifugation (1000×*g*; 10 min). The resulting supernatant was stored at −80 °C for later research.

Perfluorohexane sulfonic acid (PFHxS), PFOA, PFNA, PFOS, perfluorodecanoic acid (PFDeA), perfluoroundecanoic acid (PFUA), PFDoA, perfluoroheptanoic acid (PFHpA), and PFBS were all found in plasma samples. The analyses were carried out at Zhejiang University, employing the procedures outlined in the work of Wang et al. (2016).

PFAS levels were determined using liquid chromatography in conjunction with a tandem-mass-spectrometry ("HPLC-MS/MS, Agilent Technologies Inc, USA"). To establish reference values that encompassed a combination of nine PFAS compounds, blank fetal-bovine serum was utilized for comparison and calibration purposes. This analytical methodology allowed for the accurate measurement of PFAS levels in the study participants, and internal standards included isotope-

labeled PFOS and PFOA (^{13}C4-PFOS and ^{13}C4-PFOA).

All measurements were performed with multiple reaction monitoring (MRM) in negative electrosprayionization (ESI) mode. The quantification was conducted through the internal standard approach. The reference curve was comprised of 6 standard concentration points spanning from 0.5 ng/mL to 200 ng/mL, exhibited excellent relationship with correlation coefficients of 0.99 for all the substances. The lower limits of quantification (LOD) taken at 0.01 ng/mL for PFOA, PFDeA, PFBS and PFOS, 0.02 ng/mL for PFHxS, PFNA and PFUA, 0.03 ng/mL for PFHpA, and 0.05 ng/mL for PFDoA. Concentrations lower than the LOD were substituted by the LOD/$\sqrt{2}$ in the dataset to account for values below the detection limit. Furthermore, in subsequent analyses, PFDoA was excluded if its detection rate was lower than 80%.

2.3. Sex hormone measurement

Blood samples were collected over the first 3 days of a woman's menstrual cycle to analyze the foundational hormone profiles, which comprised follicular-stimulating-hormone (FSH), luteal hormone (LH), and estradiol (E_2). The E_2 peak levels were measured on the day of trigger with hCG. The examinations were executed at a Women's Hospital School of Medicine.

2.4. Treatment strategies and evaluation of IVF results

This process involved ovarian stimulation following the GnRH agonist protocol, and the descriptions of IVF outcomes were in accordance with our prior investigation, albeit with minor adjustments (Shen et al., 2020). In brief, a successful pregnancy was concluded by noting an elevated plasma β-hCG level and the sonographic observation of fetal heart pulsations about five weeks succeeding embryo implantation. The implantation percentage was computed as the ration of visible conception sacs to the total embryos placed. Whereas, in this study we defined live birth rate as the total deliveries with single or multiple live neonates beyond certain gestation period (24-weeks) per embryo transfer interval. Each female participant contributed one IVF cycle to this study, with all the participants having their first IVF cycle.

2.5. Statistical analysis

Statistics for constant variables were presented as means, standard deviations (SD), or the median with interquartile range (IQR) for normalized data. Additionally, we computed Spearman rank correlations between plasma PFAS concentrations in pairs.

To study the association between plasma PFAS levels and IVF effects, multifactorial combined generalized linear mixed models with unfixed intercepts was used. We identified total oocytes recovered, 2 PN (two pronuclei) zygotes, cleavage embryos, high-quality embryos and live birth were Poisson distribution and the link function was log. Specified endometrial wall thickness, E_2 peak levels and implantation (0,1/3,1/2,2/3,1) were Gaussian distribution and link function was identified. Designated Clinical pregnancy and Abortion as Binomial distribution, and the link function was logit. We utilized different statistical models for distinct variables. Linear trend analysis identified link between PFAS concentrations and IVF outcomes, while considering various factors like age, BMI, infertility diagnosis, stimulation protocol, and Basal hormone profiles. Similarly, the linkage between PFAS tertile levels and clinical findings was assessed using multivariable logistic regression. We assessed linear trends using the median values from each plasma quartile treated as continuous variables. For missing data, we use the Mean Substitution method in the analysis.

Robustness of the results was testified through: 1) limiting the analysis to single IVF cycle for each participant; 2) age characterization of less than 35 years or older than 35 years, and through protocol type (agonist vs. other) to assess alterations in effects.

Bayesian kernel machine regression (BKMR) was employed to investigate the potential joint effect estimates of a PFAS on IVF outcomes (endometrial wall thickness, E_2 peak levels, oocytes retrieved, 2 PN zygotes, cleavage embryos, high-quality embryos, clinical pregnancies, implantation, abortion, and live birth). The BKMR methodology permits appraisal of the autonomous connections of distinct PFAS mixture elements, considering overall combined mixed PFAS exposure.

The PFAS exposure–response connections were evaluated using the BKMR model (log transformed) and IVF outcomes: a) Determining overall PFAS mixture effect on IVF outcomes at median individual PFAS levels and b) Assessing dose-response of individual PFAS on IVF outcomes while fixing other PFAS at percentiles (25th, 50th, and 75th). The collective impact of PFAS combinations on IVF findings was assessed by employing the BKMR models. This involved standardizing all PFAS mixtures within the 25-75th percentile range with 5th percentile intervals and comparing them to the overall PFAS performance when standardized at the 50th percentile.

R software (version 4.2.3) was used throughout for data analysis. Marginal means were conducted using R software with the "emmeans" package (1.8.4–1) and BKMR model was conducted with the "bkmr" package (0.2.2) and the number of interactions run is 1000. A statistical value of less than 0.05 is considered to be significant.

3. Results

3.1. Demographic attributes of participants

As presented in Table 1, the current study comprised 259 participants. Women's mean age was 30.14 ± 3.79 y, ranging from 20 to 39 y. All women currently did not smoke tobacco. The mean BMI was 21.40

Table 1
Demographic characteristics and clinical characteristics among women undergoing in vitro fertilization(N = 259).

Variables	Values
Age (y)	
Mean ± SD	30.140 ± 3.793
Range	20~39
BMI (kg/m2)	
Mean ± SD	21.400 ± 2.558
Range	16.23–28.13
infertility diagnosis	
Only female infertility factor	190(78.51%)
Only male infertility factor	34(14.05%)
Unexplained	18(7.44%)
Basal hormone profiles	
Estradiol (nmol/L)	102.160 ± 55.775
FSH (IU/L)	6.573 ± 1.849
LH (IU/L)	5.172 ± 5.648
Antral follicle count	12.058 ± 4.594
Ovarian stimulation protocol	
Long GnRH agonist	142(54.82%)
GnRH antagonist protocol	88(33.98%)
Others	29(11.20%)
Fertilization procedure	
IVF	180(69.50%)
ICSI	75(28.96%)
half ICSI	4(1.54%)
Number of follicles greater than 14 mm	12.266 ± 6.299
Peak estradiol level (pmol/L)	11483.2 ± 6649.236
Gn dosage(IU)	2262.301 ± 1192.646
Endometrial thickness on the day of egg retrieval(cm)	1.105 ± 0.265
Total oocytes retrieved	12.486 ± 6.598
2 PN Zygotes	6.467 ± 4.337
Cleavage embryos	6.039 ± 4.184
High quality embryos	3.050 ± 2.263

Note: Values are represented as mean ± SD, or number (%). Percentages may not sum to 100% due to number rounding. 2 PN, two pronuclei; BMI, body mass index; CC, clomiphene citrate. GnRH, gonadotrophin releasing hormone; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; LH, luteinizing hormone; SD, standard deviation.

kg/m^2, ranging from 16.23 to 28.13. Infertility was primarily reflected as female factors in the majority of cases (78.51%), with 13.05% linked to male infertility, and 7.44% classified as unexplained infertility. In Table 1, descriptive statistics concerning participant's baseline hormone profiles and IVF findings are listed. The extended GnRH-agonist ovarian stimulation protocol (54.82%) was commonly used. Approximately, 69.5% participants underwent IVF, while 28.96 % opted for ICSI, and 1.54% chose half-ICSI. On average, female participants yielded 12.5 ± 6.6 oocytes per cycle. Furthermore, each cycle produced an average of 6.5 ± 4.3 successfully fertilized oocytes (2 PN zygotes), leading to the development of 3.1 ± 3.3 good-quality embryos by day 3.

3.2. PFAS concentration and correlation in Women's plasma

Regarding PFAS distribution and correlation in women plasma (as shown in Table 2), eight PFAS (PFHxS, PFOA, PFNA, PFOS, PFDeA, PFUA, PFHpA, and PFBS) remained noticed in over 85% of plasma samples. The PFAS distribution and LODs are shown in Table 2, with PFOA having the greatest mean concentration (19.11 ng/mL), preceding PFOS (11.37 ng/mL). Notably, PFHxS, PFOA, PFNA and PFDeA exhibited robust and positive correlations among themselves (r = 0.238–0.762, $p < 0.001$; Table S1), PFOS levels were positively linked to PFNA (r = 0.566, $p <$ 0.001; Table S1), and PFHpA was positively associated with those of PFOA and PFBS, respectively (r = 0.219, $p <$ 0.001; r = 0.226, $p <$ 0.001; Table S1).

4. Associations of individual plasma PFAS with IVF outcomes

In multivariable generalized linear mixed models, accounting for female participant's age, BMI, infertility diagnosis, stimulation protocol, and baseline hormonal profiles, this study identified statistically significant connections between plasma PFNA levels and decreased numbers of total retrieved oocytes[12.486(95%CI: 0.446,25.418), p_{trend} = 0.017], 2 PN zygotes [6.467(95%CI: 2.034,14.968) p_{trend} = 0.007], and cleavage embryos [6.039(95%CI: 2.162,14.240) p_{trend} = 0.008] (Table 3).

Specifically, females in the highest plasma PFNA concentration quartile (ranging from 2.337 to 32.191 ng/mL) yielded an average of 1.33 fewer retrieved oocytes, 0.88 fewer 2 PN zygotes, and 0.79 fewer cleavage embryos compared to females in the lowest PFNA quartile (0.184–1.127 ng/mL), for which 95% confidence intervals were (10.00, 12.96), (4.56, 6.24), and (4.25,5.84), respectively. Likewise, a consistent decrease in the number of retrieved 2 PN zygotes and cleavage embryos was observed with increasing PFOS concentration [6.467(95% CI: 2.034,14.968), p trend = 0.009 and 6.039(95%CI: 2.162,14.240), p trend = 0.031 respectively], indicating statistical significance. In the highest plasma PFOS concentration quartile, female participants had 0.71 fewer 2 PN zygotes and 0.47 fewer cleavage embryos compared to females in the lowest quartile, respectively. However, the difference for the total number of retrieved oocytes between the groups was not significant (Table 3). Significant dose-response associations of plasma PFOA concentrations and E_2 (peak) levels are shown in Table 3(p_{trend} = 0.016). This study also explored the impact of PFAS exposure on females experiencing their initial fresh ET cycles (n = 160). After adjusting for females age, BMI, infertility diagnosis, stimulation protocol, and baseline hormone profiles, there was no observable dose-response correlation between plasma PFAS concentrations and reproductive outcomes (refer to Table S2).

However, this study observed a negative association between PFHxS concentrations and clinical pregnancy during the initial cycles of frozen ET [n = 80,0.525(95%CI:0.410,0.640), p trend = 0.021, Table S3]. Multivariable generalized linear mixed models did not suggest associations of the other PFAS with clinical pregnancy, implantation, abortion and live birth.

Table 2
Concentrations (ng/mL) of detected PFAS in 259 women plasma.

PFAS	Detection(%)	Mean ± SD	Median (Q1, Q3)
PFHxS	100	1.796 ± 1.321	1.295(0.811,2.421)
PFOA	100	19.11 ± 13.187	15.645(8.411,26.438)
PFNA	100	2.141 ± 2.909	1.620(1.127,2.337)
PFOS	95.75	11.37 ± 28.038	4.978(0.998,10.562)
PFDeA	96.91	2.799 ± 4.573	1.495(0.787,2.801)
PFUA	93.82	1.735 ± 6.555	0.207(0.079,0.854)
PFHpA	100	0.293 ± 0.608	0.148(0.117,0.178)
PFBS	95.75	0.056 ± 0.079	0.037(0.030,0.053)

4.1. Associations of PFAS mixture with IVF outcomes

To investigate the joint effect of PFAS mixtures, this study conducted a confounder-adjusted BKMR model analysis. We showed the impact of the PFAS mixtures on the good-quality embryos, the 2 PN zygotes and cleavage embryos through BKMR analysis. (Fig. 1A, Fig. S1A, Fig. S2A, respectively). Univariate exposure-response relationship for 8 PFAS (Fig. 1C, Fig. S1C, Fig. S2C) represent the link between these chemicals and high-quality embryos, the 2 PN zygotes or cleavage embryos in IVF when all other PFAS held at median levels. Individual response relationship for the 8 kinds of PFAS are depicted in Fig. 1D, Fig. S1D and Fig. S2D, respectively.

The results of this study indicated that there might be a negative correlation between plasma PFAS mixtures and the quantities of good-quality embryos, 2 PN zygotes, and cleavage embryos.(as presented in Fig. 2, Table 4; Fig. S1B, Table S5; Fig. S2B, Table S7, respectively). For instance, when comparing the 75th percentile of the PFAS mixture levels fixed at the exposure distribution with the 50th percentile, we observed a decreased posterior mean estimate of high-quality embryos (−0.13%; 95% CI: −0.57, 0.003) (Table 4). Furthermore, this study investigated the distinct contributions of individual PFAS components to the overall association of PFAS mixtures. Our analysis revealed that PFUA and PFOA were notably correlated with a reduced number of good-quality embryos, while all other PFAS held at the 25th, 50th, and 75th percentiles (Table S5). Through the estimation of posterior inclusion probabilities (PIPs), BKMR identified PFOA as the primary contributor to the overall trend and its correlation with lowered 2 PN zygote numbers (Table S6). Specifically, the individual fluctuations in PFOA levels from 25th to 75th percentiles were −0.39(95% CI: 1.35, 0.58), −0.37 (95% CI: 1.33, 0.59), −0.36 (95% CI: 1.33, 0.61) lower odds of 2 PN zygotes, with other PFAS held at their median concentrations (Table S6). This study also examined intermediate outcomes, such as the number of cleavage embryos, and found that the association patterns remained similar (Table S8). This study did not observe evidence of plasma PFAS mixture with endometrial wall thickness, E_2 peak level, clinical pregnancy, implantation, abortion and live birth (Tables S9–14) (see Fig. 3).

5. Discussion

5.1. Key findings summary

In this study, we detected clear relationships between several PFAS levels and IVF findings. The analysis undertaken of PFAS as a composite revealed a possible adverse relationship between the PFAS mixture and a reduction in the quantities of good-quality embryos, 2 PN zygotes, and cleavage embryos. Furthermore, PFOA, PFOS and PFUA appeared to dominate the association. Nonetheless, no interrelationship was observed among the PFAS and implantation, clinical pregnancy or live birth in IVF.

The data generated in this study suggests that PFOA and PFOS were the predominant PFAS detected in humans, which is consistent with prior research (Cariou et al., 2015; Velez et al., 2015; Li et al., 2017). The median PFOA levels in this study (15.6 ng/mL) and other study conducted in Shanghai (14.7 ng/mL) were found elevated compared to

Table 3
Plasma concentrations of PFAS in relation to ovarian stimulation outcomes among 259 women contributing to fresh IVF cycles in the study.

PFAS	E2(peak) pmol/L	endometrial thickness (cm)	Total oocytes retrieved	2 PN Zygotes	Cleavage embryos	High quality embryos
PFHxS						
Q1(0.203–0.811)	12247.77(10488.75,14006.79)	1.12(1.05, 1.19)	12.03(10.36,13.71)	6.68(5.47, 7.89)	6.18(5.02,7.35)	2.89(2.25,3.53)
Q2(0.811–1.295)	11264.15(9696.39, 12831.92)	1.08(1.02, 1.13)	12.08(10.51,13.64)	6.51(5.45, 7.57)	6.16(5.12,7.19)	2.91(2.28,3.53)
Q3(1.295–2.421)	11123.59(9530.45, 12716.73)	1.12(1.05, 1.18)	12.8(11.05,14.54)	6.06(5.04,7.08)	5.69(4.73,6.64)	3.06(2.55,3.58)
Q4(2.421–7.616)	11288.77(9576.31, 13001.22)	1.11(1.04, 1.18)	13.05(11.45,14.64)	6.62(5.59, 7.64)	6.12(5.12,7.13)	3.34(2.89,3.79)
p-Trend	0.1237	0.4804	0.0549	0.6583	0.6352	0.1232
PFOA						
Q1(3.339–8.411)	12401.63(10700.36, 14102.90)	1.12(1.06, 1.19)	12.71(10.95, 14.47)	6.46(5.32, 7.60)	6.06(4.96, 7.16)	3.08(2.39,3.76)
Q2(8.411–15.645)	11345.72(9633.38,13058.07)	1.10(1.04, 1.17)	12.31(10.69, 13.93)	6.35(5.28, 7.43)	5.88(4.85, 6.90)	2.74(2.15, 3.33)
Q3(15.645–26.438)	11970.4(10312.80,13628.00)	1.08(1.02, 1.13)	12.97(11.26, 14.68)	6.48(5.42, 7.53)	6.06(5.01, 7.12)	3.09(2.65,3.53)
Q4(26.438–62.296)	10174.79(8659.02,11690.57)	1.11(1.04, 1.19)	11.95(10.48, 13.43)	6.58(5.53, 7.63)	6.16(5.15, 7.16)	3.30(2.80,3.79)
p-Trend	**0.016***	0.4595	0.4193	0.7393	0.7333	0.2992
PFNA						
Q1(0.184–1.127)	11197.09(9559.39, 12834.8)	1.08(1.02, 1.15)	12.81(11.26, 14.37)	6.28(5.27, 7.29)	5.84(4.87,6.82)	2.75(2.20, 3.30)
Q2(1.127–1.620)	11951.46(10200.34,13702.58)	1.14(1.06, 1.21)	13.17(11.54, 14.79)	7.64(6.47, 8.80)	7.23(6.07,8.40)	3.65(3.01, 4.29)
Q3(1.620–2.337)	11697.92(9867.12,13528.7)	1.06(0.99,1.13)	12.48(10.60, 14.37)	6.53(5.33, 7.73)	6.03(4.89,7.17)	2.92(2.40, 3.44)
Q4(2.337–32.191)	11085.23(9685.85, 12484.61)	1.14(1.08,1.2)	11.48(10.00, 12.96)	5.40(4.56, 6.24)	5.05(4.25,5.84)	2.86(2.35, 3.37)
p-Trend	0.9666	0.8584	**0.0165***	**0.0073***	**0.008***	0.6664
PFOS						
Q1(0.007–0.998)	10985.42(9373.32, 12597.52)	1.09(1.03, 1.15)	12.92(11.44, 14.4)	6.73(5.71, 7.75)	6.12(5.13, 7.12)	2.86(2.31, 3.41)
Q2(0.998–4.978)	12498.25(10777.88, 14218.61)	1.09(1.02, 1.16)	12.71(11.02, 14.41)	7.30(6.11, 8.49)	6.94(5.74, 8.13)	3.35(2.73, 3.97)
Q3(4.978–10.562)	10307.47(8827.34, 11787.59)	1.12(1.05, 1.19)	12.38(10.68, 14.07)	5.80(4.92, 6.68)	5.44(4.62, 6.26)	3.09(2.60, 3.59)
Q4 (10.562–320.752)	12115.92(10351.73, 13880.12)	1.11(1.05, 1.18)	11.94(10.24, 13.63)	6.02(4.86, 7.17)	5.65(4.55, 6.74)	2.89(2.32, 3.47)
p-Trend	0.8354	0.7904	0.0942	**0.0094***	**0.0313***	0.8602
PFDeA						
Q1(0.007–0.787)	11361.54(9683.36, 13039.72)	1.12(1.05, 1.18)	13.22(11.69, 14.74)	6.83(5.68, 7.97)	6.34(5.24, 7.44)	2.86(2.24, 3.48)
Q2(0.787–1.495)	10673.27(9323.72, 12022.82)	1.11(1.04, 1.18)	12.41(10.87, 13.95)	6.76(5.88, 7.63)	6.28(5.43, 7.12)	3.15(2.63, 3.67)
Q3(1.495–2.801)	11619.74(9793.45, 13446.03)	1.10(1.02, 1.17)	11.94(10.09, 13.79)	5.78(4.70, 6.86)	5.51(4.45, 6.56)	3.02(2.45, 3.59)
Q4(2.801–37.998)	12299.53(10551.28, 14047.78)	1.09(1.04, 1.15)	12.39(10.75, 14.03)	6.50(5.30, 7.70)	6.03(4.87, 7.19)	3.17(2.63, 3.72)
p-Trend	0.2224	0.3275	0.1343	0.1649	0.2113	0.4145
PFUA						
Q1(0.014–0.079)	10984.98(9560.61, 12409.36)	1.13(1.06, 1.2)	12.58(11.11, 14.04)	6.11(5.15, 7.07)	5.64(4.73, 6.55)	2.64(2.14, 3.14)
Q2(0.079–0.207)	11164.2(9481.02, 12847.38)	1.10(1.04, 1.16)	12.34(10.75, 13.93)	6.72(5.60, 7.85)	6.25(5.13, 7.36)	3.45(2.84, 4.05)
Q3(0.207–0.854)	11444.29(9875.74, 13012.85)	1.09(1.03, 1.15)	12.20(10.49, 13.91)	6.48(5.38, 7.58)	6.05(5.05, 7.05)	2.94(2.39, 3.48)
Q4(0.854–59.015)	12324.00(10416.35, 14231.65)	1.10(1.03, 1.17)	12.83(11.03, 14.63)	6.55(5.42, 7.69)	6.22(5.08, 7.35)	3.17(2.58, 3.76)
p-Trend	0.3894	0.4057	0.7495	0.4463	0.2673	0.2726
PFHpA						
Q1(0.041–0.117)	11809.23(9964.86, 13653.61)	1.08(1.01, 1.15)	12.97(11.20, 14.74)	6.26(5.28, 7.24)	5.89(4.95, 6.83)	3.03(2.44, 3.62)
Q2(0.117–0.148)	11787.39(10185.45, 13389.34)	1.14(1.07, 1.21)	12.4(10.84, 13.97)	6.57(5.49, 7.65)	6.03(5.00, 7.06)	3.31(2.71, 3.91)
Q3(0.148–0.178)	11019.05(9380.22, 12657.87)	1.10(1.05, 1.16)	12.65(10.88, 14.43)	6.52(5.41, 7.64)	6.17(5.07, 7.28)	2.86(2.37, 3.35)
Q4(0.178–7.464)	11295.28(9752.77, 12837.79)	1.09(1.03, 1.16)	11.92(10.47, 13.38)	6.52(5.36, 7.67)	6.06(4.96, 7.17)	2.98(2.43, 3.54)
p-Trend	0.6340	0.8483	0.1416	0.6126	0.6319	0.5380
PFBS						
Q1(0.007–0.030)	10831.77(9262.01, 12401.53)	1.12(1.04, 1.20)	12.26(10.60, 13.93)	6.61(5.47, 7.74)	6.13(5.11, 7.15)	3.16(2.59, 3.74)

(*continued on next page*)

Table 3 (*continued*)

PFAS	E2(peak) pmol/L	endometrial thickness (cm)	Total oocytes retrieved	2 PN Zygotes	Cleavage embryos	High quality embryos
Q2(0.030–0.037)	11820.52(10187.69, 13453.35)	1.07(1.01, 1.13)	12.62(11.01, 14.24)	6.64(5.60, 7.67)	6.23(5.21, 7.24)	3.27(2.72, 3.82)
Q3(0.037–0.053)	10502.19(9081.68, 11922.7)	1.09(1.04, 1.15)	11.81(10.34, 13.28)	5.84(4.85, 6.83)	5.53(4.53, 6.53)	2.86(2.24, 3.47)
Q4(0.053–0.748)	12840.37(10885.37, 14795.36)	1.14(1.07, 1.21)	13.30(11.47, 15.13)	6.84(5.68, 8)	6.30(5.16, 7.44)	2.92(2.43, 3.41)
p-Trend	0.6905	0.5617	0.2639	0.9185	0.8692	0.2344

Note: The mean values and 95% confidence interval of oocytes/embryo counts were present in the table. Models were run using Poisson regression with log link. The lowest tertile of plasma PFAS content were considered as reference. Models adjusted for women's age, BMI, infertility diagnosis, stimulation protocol, and Basal hormone profiles.

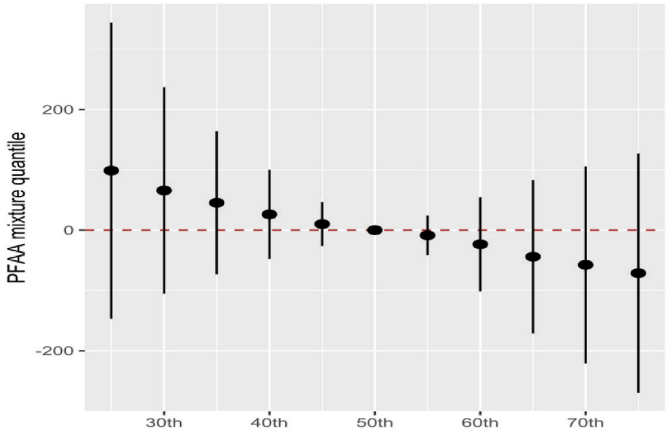

Fig. 1. The result of 3000 iterations.

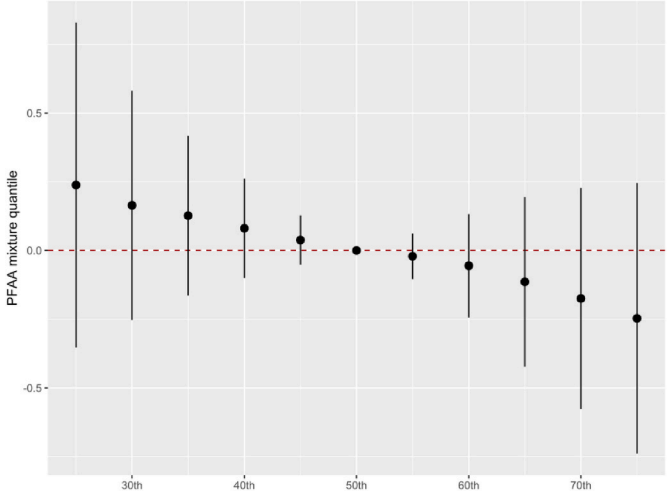

Fig. 2. The result of 10000 iterations.

values cited in previous researches (Louis et al., 2015; Raymer et al., 2012). The discrepancies in levels of different types of PFAS might be attributed to: varying exposure sources in regions (Pan et al., 2014), various dietary sources of PFAS exposure (Domingo et al., 2017), as well as the diverse composition of study participants. Due to concerns related to human health risks, PFOA and PFOS have been restricted or banned in many Western countries. However, there have been no relevant public policies announced in China so far (Lim et al., 2011; Karwacka et al., 2019).

5.2. Comparison of previous research evaluating individual PFAS and IVF results

Examination of PFAS exposure and IVF findings in prior studies has yielded mixed findings. In line with findings of this study, another Chinese cohort (n = 96 couples) discovered a link between higher mother's serum PFOA contents and a lower number of developed oocytes and good-quality embryos. It is important to note, though, that the authors of that other study did not furnish details regarding the combined impact of PFAS mixtures (Ma et al., 2021). A second cohort study in China also found that higher PFOA or PFOS were related with fewer good-quality embryos from intermediate IVF outcomes; however, the evidence generated failed to establish the association involving PFAS and sexual results (Zeng et al., 2023b). Differing from our findings, research conducted in Australia found no significant connection between eight distinct PFAS compounds in follicular fluid and the fertilization rate (Kim et al., 2020). Similarly, Hong et al. in China reported an absence of correlation between concentrations of PFAS follicular fluid and IVF results (Hong et al., 2022b). On the contrary, a study in Belgium arrived at contrasting results. The authors employed a principal component analysis, and it indicated that when considering various factors including maturity, estradiol levels, BMI, male subfertility, and the prevalence of other organic compounds, overall PFAS content in follicular fluid found to be linked to accelerated fertilization rate (Petro et al., 2014). Overall, our results of negative associations between several PFAS and the variety of matured embryos and oocytes, which are of outstanding value, 2 PN zygotes, and cleavage embryos are in line with some previously reported findings.

5.3. Contrasting with previous research on PFAS mixtures and IVF results

While individuals have experienced various PFAS, limited research has focused on quantifying the collective effects of PFAS mixtures on IVF findings. Our study, as a first report of undergoing research, suggests that PFAS mixtures might have a negative impact on women's fertility by influencing both the quantity and quality of embryos. Applying BKMR and quantile approaches, we identified analogous links between PFAS and IVF results in our examination of PFAS, whether considered individually or as a composite.

Furthermore, within our investigation, we discerned that the overarching pattern exhibited substantial statistical significance within singular models. Notably, females with PFNA levels in the uppermost quartile displayed the lowest total oocyte retrieval. The achievement of fertilization and early embryo growth is intimately linked to the developmental capacity of the oocyte (Schier, 2007). Additionally, animal experimental studies in vitro demonstrated that exposure to PFOS can potentially compromise quality of the oocyte through interfering with ovarian meiotic competence and proliferation (Chen et al., 2021; Wolf et al., 2012; Sant et al., 2018).

Studies have also demonstrated that PFOS and PFNA can hinder oocyte maturation through the interruption of mitochondrial activity, the induction of oxidative stress, and the initiation of oocyte apoptosis

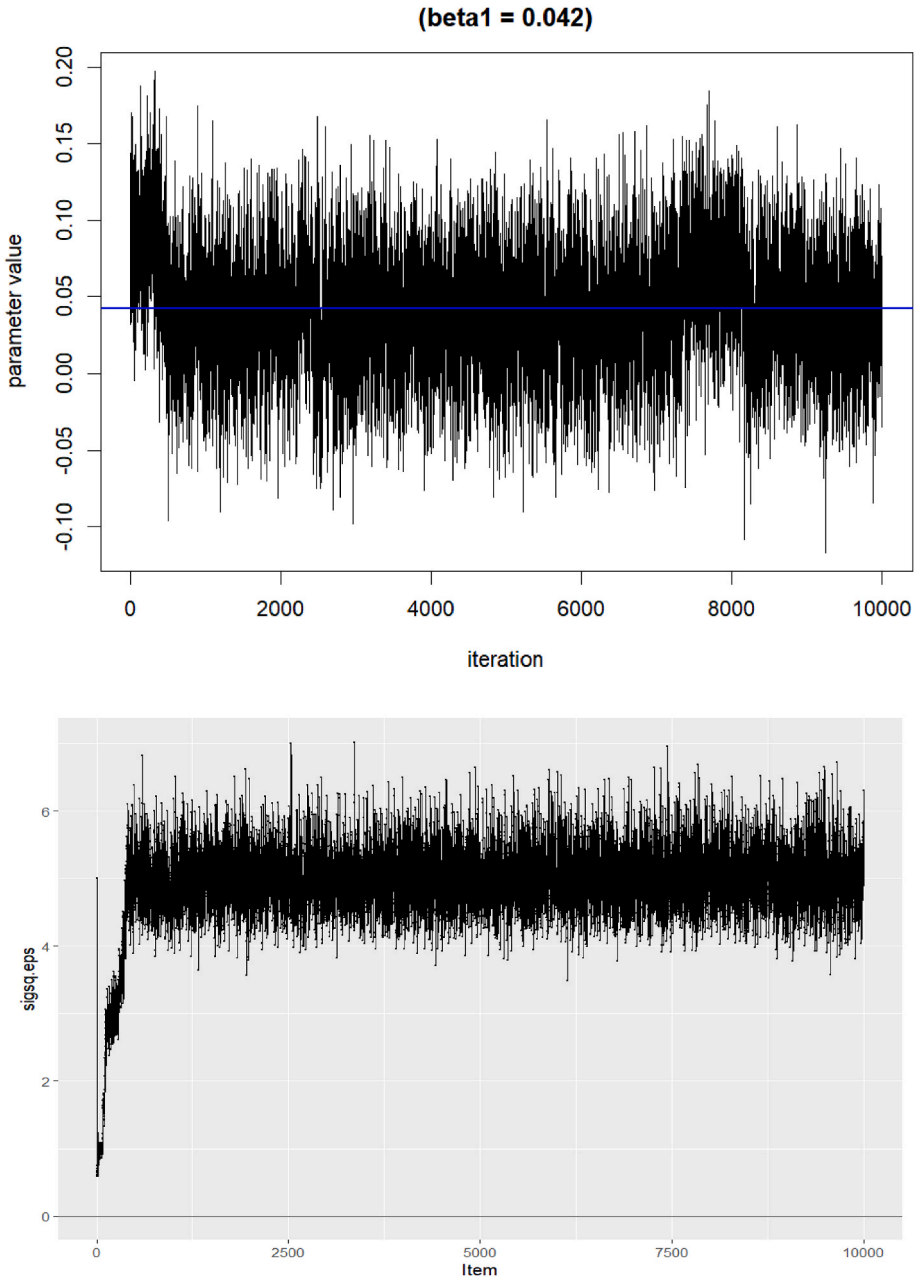

Fig. 3. The value of Sigsq. eps and β after approximately 1000 iterations.

(Chen et al., 2021; Jiao et al., 2021). In a laboratory setting using bovine oocytes, Hallberg et al. ascertained that early embryo development was influenced by exposure to PFOS levels pertinent to humans, potentially leading to detrimental effects on subsequent development (Hallberg et al., 2021). Therefore, evidence suggests that PFAS may impact the oocyte potential development and the process of fertilization, which is a cause for concern. Further epidemiological analysis is needed to establish the possible adverse interactions between exposure to PFAS and ovulation.

In addition, the results from our investigation suggest that there was a lack of correlation between the outcomes of initial frozen ET cycles and the PFAS mixtures. However, we found that there was an inverse relationship between PFHxS concentrations and clinical pregnancy rate in individual models from initial frozen ET cycles (trend $p = 0.02$). Despite conflicting results, in our study it appears that decreased implantation rate occurs in high PFAS-exposure women. The failure of embryo implantation can be attributed to factors such as oocyte maturation, embryo quality, impaired endometrial receptivity, and deficient embryo-endometrium signaling (Xiao et al., 2011). Thus, we can suggest that prolonged exposure to PFAS may have a more significant effect on embryos or endometrium than short-term exposure on women's implantation.

5.4. Biological mechanisms

The ovary's principal functions encompass the creation, development, and discharge of the female germ cell (oocyte), while also producing gender hormones and peptide compounds that regulate reproduction-related functions (Cavalcante et al., 2023). Though a particular species study has revealed that PFAS can contribute to the development of follicles in the ovary and produce oocytes (Chen et al., 2021; Hallberg et al., 2021; Dominguez et al., 2016), the exact mechanistic understanding of PFAS-induced fluctuations on the human reproductive system need to be further uncovered. Endometriosis

Table 4
Posterior mean estimates of the overall effect estimates of PFAS mixture associated with the high-quality embryo from the BKMR model. [a]

PFAS mixture at specific quantile	Posterior mean estimates (95% CI) [b]
25th	00.19(-0.34,00.72)
30th	00.13(-0.24,00.50)
35th	00.10(-0.16,00.35)
40th	00.05(-0.11,00.21)
45th	00.03(-0.05,00.11)
50th	00.00(00.00,00.00)
55th	−0.01(-0.08,00.07)
60th	−0.03(-0.19,00.14)
65th	−0.06(-0.33,00.21)
70th	−0.08(-0.43,00.27)
75th	−0.13(-0.57,00.31)

[a] Models adjusted for women's age, BMI, infertility diagnosis, stimulation protocol, and Basal hormone profiles.
[b] Overall posterior mean estimates of the PFAS mixture, defined as the difference in the response when the PFAS mixture concentration was fixed at a specific quantile (ranging from 25th to 75th percentiles), as compared to when the mixture was fixed at the median value.

appears to be confirmed by PFBS intake, consequently raising the possibility of female infertility (Wang et al., 2017). Based on available findings, PFAS exposure has the capacity to promote cell death in adult granulosa cells of the ovary and interfere with steroid synthesis in both granulosa and porcine theca cells, regardless of gonadotropic stimulation (Zhou et al., 2020; Chaparro-Ortega et al., 2018). Research has documented a link between elevated PFOS levels and decreased estradiol and progesterone levels (Barrett et al., 2015). In parallel, serum testosterone exhibited a noteworthy correlation with the concentrations of PFOA, PFHxS, and PFNA (Heffernan et al., 2018). Specifically, PFOS are recognized as a substance having negative consequences on reproduction (Ding et al., 2020; Tsuda, 2016). Hence, evidence generated in this study can also contribute to raise public awareness on the deleterious effects of certain PFAS on human healthy reproduction.

The correlation between PFAS exposure and a reduced quantity of high-quality embryos could be explained by the activation of peroxisome proliferator–activated receptors (PPARs). PPARs have a significant role in male and female germ cell function and oocyte maturation (Wolf et al., 2012; Maradonna et al., 2018). The interaction of PFAS with PPARs might disrupt steroidogenesis response elements, leading to negative effects on follicular development and, consequently, embryo development. However, the PFAS doses delivered in animal research exceeded the PFAS amounts frequently observed in the general human population, which may possibly induce a variety of harm routes and mechanisms. In purview of possible threat of PFAS to human fertility, forthcoming research should incorporate experimental studies involving PFAS doses mirroring typical human exposure levels and combinations of these substances.

5.5. Strengths and limitations

In this cohort research, we identified connections between PFAS mixtures and both fertilization and development of high-quality embryos among women undergoing IVF. Subsequent studies need to delve into both the individual and combined impacts of PFAS on fertility status of women throughout the reproductive journey. Additionally, it is necessary to scrutinize the consistency of these results across different population groups. Further efforts also are needed to elucidate the potential mechanisms underlying the reproductive effects associated with PFAS. Our study faced a limitation in which the analysis to only cycles with fresh embryo transferred may induce a selection bias. And, we did not calculate the group PIPs and conditional PIPs, that might affect the accuracy of the results. Additionally, we have considered recent evidence on research trends and methods while planning this study (Antunes, 2022; Chen et al., 2022; Chen and Qin, 2023; Dsouza, 2022; Dsouza et al., 2023; Ferreira et al., 2023; Gao et al., 2024; Han et al., 2023; Jacennik et al., 2022; Jia et al., 2023; Kehinde et al., 2023; Li et al., 2022; Lloyd Williams, 2022; Loureiro Pais Batista et al., 2023; Monachino, 2022; Moreira, 2022; Nguyen, 2022; Niu, 2023; Song and Xie, 2023; Sun et al., 2023; Tian et al., 2023; Wang et al., 2024; Wei, 2023; Wei and Xue, 2022; Zhang et al., 2022a,b,2023a,b)

6. Conclusions

In this observational research, we found that PFAS mixtures may be associated with fertilization and high-quality embryos in women undergoing in vitro fertilization.

Subsequent research endeavors ought to delve deeper into both the individual and cumulative impacts of PFAS on human reproductive capabilities throughout the entire reproductive timeline. Moreover, it is important to assess the repeatability of these outcomes within various demographic groups. Additional research is required to uncover the potential mechanisms underlying the reproductive effects associated with PFAS.

Ethical approval

This work has received approval for research ethics from the Women's Hospital School of Medicine at Zhejiang university (No. 20130044) and a proof/certificate of approval is available upon request. The recruited study participants provided written informed consent prior to their enrolment.

Funding

This work was supported by the National Key Research and Development Program of China (no. 2018YFC1004900).

CRediT authorship contribution statement

Juan Shen: Writing – original draft, Investigation, Conceptualization. **Yuchan Mao:** Methodology. **Hongyan Zhang:** Data curation. **Hangying Lou:** Formal analysis. **Ling Zhang:** Investigation. **Joaquim Paulo Moreira:** Writing – review & editing, Validation. **Fan Jin:** Supervision, Funding acquisition.

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.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2024.124474.

References

Antunes, V., 2022. On nursing research and evidence-based practice: topics for researchers and practitioners. International Healthcare Review (online) 1 (1). https://doi.org/10.56226/ihr.v1i1.12.
Aro, R., Eriksson, U., Karrman, A., Yeung, L., 2021. Organofluorine mass balance analysis of whole blood samples in relation to gender and age. Environ. Sci. Technol. 55 (19), 13142–13151.
Balk, F., Winkens, P.K., Ribbenstedt, A., Gomis, M.I., Filipovic, M., Cousins, I.T., 2019. Children's exposure to perfluoroalkyl acids - a modelling approach. Environ Sci Process Impacts 21 (11), 1875–1886.

Barrett, E.S., Chen, C., Thurston, S.W., Haug, L.S., Sabaredzovic, A., Fjeldheim, F.N., Frydenberg, H., Lipson, S.F., Ellison, P.T., Thune, I., 2015. Perfluoroalkyl substances and ovarian hormone concentrations in naturally cycling women. Fertil. Steril. 103 (5), 1261–1270.

Cariou, R., Veyrand, B., Yamada, A., Berrebi, A., Zalko, D., Durand, S., Pollono, C., Marchand, P., Leblanc, J.C., Antignac, J.P., Le Bizec, B., 2015. Perfluoroalkyl acid (PFAA) levels and profiles in breast milk, maternal and cord serum of French women and their newborns. Environ. Int. 84, 71–81.

Cavalcante, M.B., Sampaio, O., Camara, F., Schneider, A., de Avila, B.M., Prosczek, J., Masternak, M.M., Campos, A.R., 2023. Ovarian aging in humans: potential strategies for extending reproductive lifespan. Geroscience 45 (4), 2121–2133.

Chaparro-Ortega, A., Betancourt, M., Rosas, P., Vazquez-Cuevas, F.G., Chavira, R., Bonilla, E., Casas, E., Ducolomb, Y., 2018. Endocrine disruptor effect of perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) on porcine ovarian cell steroidogenesis. Toxicol. Vitro 46, 86–93.

Chen, S., Qin, Y., 2023. On ethics, biomedical education and health promotion: international and Chinese perspectives. International Healthcare Review (online). https://doi.org/10.56226/46.

Chen, Y., Zhou, L., Xu, J., Zhang, L., Li, M., Xie, X., Xie, Y., Luo, D., Zhang, D., Yu, X., Yang, B., Kuang, H., 2017. Maternal exposure to perfluorooctanoic acid inhibits luteal function via oxidative stress and apoptosis in pregnant mice. Reprod. Toxicol. 69, 159–166.

Chen, J., Miao, Y., Gao, Q., Cui, Z., Xiong, B., 2021. Exposure to perfluorooctane sulfonate in vitro perturbs the quality of porcine oocytes via induction of apoptosis. Environ. Pollut. 284, 117508.

Chen, Y., Moreira, P., Liu, W., Monachino, M., Nguyen, T.L.H., Wang, A., 2022. Is there a gap between artificial intelligence applications and priorities in health care and nursing management? J. Nurs. Manag. 1–7. https://doi.org/10.1111/jonm.13851.

Cohen, Nathan J., Yao, Meizhen, Midya, Vishal, India-Aldana, Sandra, Mouzica, Tomer, Andra, Syam S., Narasimhan, Srinivasan, Meher, Anil K., Arora, Manish, Chan, Jerry Kok Yen, Chan, Shiao-Yng, Loy, See Ling, Minguez-Alarcon, Lidia, Oulhote, Youssef, Huang, Jonathan, Valvi, Damaskini, 2023. Exposure to perfluoroalkyl substances and women's fertility outcomes in a Singaporean population-based preconception cohort. Sci. Total Environ. 873 (2023), 162267 https://doi.org/10.1016/j.scitotenv.2023.162267. ISSN 0048-9697.

Cox, C.M., Thoma, M.E., Tchangalova, N., Mburu, G., Bornstein, M.J., Johnson, C.L., Kiarie, J., 2022. Infertility prevalence and the methods of estimation from 1990 to 2021: a systematic review and meta-analysis. Hum Reprod Open 4, hoac051.

Di Nisio, A., Rocca, M.S., Sabovic, I., De Rocco, P.M., Corsini, C., Guidolin, D., Zanon, C., Acquasaliente, L., Carosso, A.R., De Toni, L., Foresta, C., 2020. Perfluorooctanoic acid alters progesterone activity in human endometrial cells and induces reproductive alterations in young women. Chemosphere 242, 125208.

Ding, N., Harlow, S.D., Randolph, J.J., Loch-Caruso, R., Park, S.K., 2020. Perfluoroalkyl and polyfluoroalkyl substances (PFAS) and their effects on the ovary. Hum. Reprod. Update 26 (5), 724–752.

Domingo, J.L., Nadal, M., 2017. Per- and polyfluoroalkyl substances (PFASs) in food and human dietary intake: a review of the recent scientific literature. J. Agric. Food Chem. 65 (3), 533–543.

Dominguez, A., Salazar, Z., Arenas, E., Betancourt, M., Ducolomb, Y., Gonzalez-Marquez, H., Casas, E., Teteltitla, M., Bonilla, E., 2016. Effect of perfluorooctane sulfonate on viability, maturation and gap junctional intercellular communication of porcine oocytes in vitro. Toxicol. Vitro 35, 93–99.

Dsouza, B., 2022. On sustainable health systems: a research emergency in pandemic times. International Healthcare Review (online) 1 (1). https://doi.org/10.56226/ihr.v1i1.7.

Dsouza, B., Prabhu, R., Unnikrishnan, B., Ballal, S., Mundkur, S.C., Chandra Sekaran, V., Shetty, A., Moreira, Paulo, 2023. Effect of educational intervention on knowledge and level of adherence among hemodialysis patients: a randomized controlled trial. Glob Health Epidemiol Genom 2023 (2023 Mar 31), 4295613. https://doi.org/10.1155/2023/4295613. PMID: 37033597; PMCID: PMC10081894. https://ops.hindawi.com/author/4295613/.

Feng, X., Wang, X., Cao, X., Xia, Y., Zhou, R., Chen, L., 2015. Chronic exposure of female mice to an environmental level of perfluorooctane sulfonate suppresses estrogen synthesis through reduced histone H3K14 acetylation of the StAR promoter leading to deficits in follicular development and ovulation. Toxicol. Sci. 148 (2), 368–379.

Ferreira, J., Horta, P., Geada, F., 2023. Internal Audit Process in eHealth: a case study. International Healthcare Review (online). https://doi.org/10.56226/50.

Gao, Y., Zhang, S., Zhao, Y., Yang, T., Moreira, P., Sun, G., 2024. Reduction of retinal vessel density in non-exudative macular neovascularization: a retrospective study. Front. Med. 10, 1219423 https://doi.org/10.3389/fmed.2023.1219423.

Giulivo, M., Lopez, D.A.M., Capri, E., Barcelo, D., 2016. Human exposure to endocrine disrupting compounds: their role in reproductive systems, metabolic syndrome and breast cancer. A review. Environ. Res. 151, 251–264.

Green, M.P., Harvey, A.J., Finger, B.J., Tarulli, G.A., 2021. Endocrine disrupting chemicals: impacts on human fertility and fecundity during the peri-conception period. Environ. Res. 194, 110694.

Hallberg, I., Persson, S., Olovsson, M., Sirard, M.A., Damdimopoulou, P., Ruegg, J., Sjunnesson, Y., 2021. Perfluorooctane sulfonate (PFOS) exposure of bovine oocytes affects early embryonic development at human-relevant levels in an in vitro model. Toxicology 464, 1–15.

Han, T., Han, M., Moreira, P., Song, H., Li, P., Zhang, Z., 2023. Association between specific social activities and depressive symptoms among older adults: a study of urban-rural differences in China. Front. Public Health 11, 1099260. https://doi.org/10.3389/fpubh.2023.1099260.

Heffernan, A.L., Cunningham, T.K., Drage, D.S., Aylward, L.L., Thompson, K., Vijayasarathy, S., Mueller, J.F., Atkin, S.L., Sathyapalan, T., 2018. Perfluorinated alkyl acids in the serum and follicular fluid of UK women with and without polycystic ovarian syndrome undergoing fertility treatment and associations with hormonal and metabolic parameters. Int. J. Hyg Environ. Health 221 (7), 1068–1075.

Hjermitslev, M.H., Long, M., Wielsoe, M., Bonefeld-Jorgensen, E.C., 2020. Persistent organic pollutants in Greenlandic pregnant women and indices of foetal growth: the ACCEPT study. Sci. Total Environ. 698, 134118.

Hong, Aobo, Zhuang, Lili, Cui, Wenxuan, Lu, Qun, Yang, Pan, Su, Shu, Wang, Bin, Zhang, Guohuan, Chen, Da, 2022a. Per- and polyfluoroalkyl substances (PFAS) exposure in women seeking in vitro fertilization-embryo transfer treatment (IVF-ET) in China: blood-follicular transfer and associations with IVF-ET outcomes. Sci. Total Environ. 838 (Part 3), 156323 https://doi.org/10.1016/j.scitotenv.2022.156323, 2022.

Hong, A., Zhuang, L., Cui, W., Lu, Q., Yang, P., Su, S., Wang, B., Zhang, G., Chen, D., 2022b. Per- and polyfluoroalkyl substances (PFAS) exposure in women seeking in vitro fertilization-embryo transfer treatment (IVF-ET) in China: blood-follicular transfer and associations with IVF-ET outcomes. Sci. Total Environ. 838 (Pt 3), 156323.

Jacennik, B., Zawadzka-Gosk, E., Moreira, J.P., Glinkowski, W.M., 2022. Evaluating patients' experiences with healthcare services: extracting domain and language-specific information from free-text narratives. Int. J. Environ. Res. Publ. Health 19, 10182. https://doi.org/10.3390/ijerph191610182.

Jia, X., Tang, X., Li, Y., Moreira, Paulo, 2023. Update of dialysis initiation timing in end stage kidney disease patients: is it a resolved question? A systematic literature review. BMC Nephrol. 24, 162. https://doi.org/10.1186/s12882-023-03184-4, 2023.

Jiao, X., Liu, N., Xu, Y., Qiao, H., 2021. Perfluorononanoic acid impedes mouse oocyte maturation by inducing mitochondrial dysfunction and oxidative stress. Reprod. Toxicol. 104, 58–67.

Karwacka, A., Zamkowska, D., Radwan, M., Jurewicz, J., 2019. Exposure to modern, widespread environmental endocrine disrupting chemicals and their effect on the reproductive potential of women: an overview of current epidemiological evidence. Hum. Fertil. 22 (1), 22–25.

Kehinde, O., Dixon-Lawson, K., Mendelsohn, A., 2023. On community pharmacists and promotion of lifestyle modification in adults with hypertension: practice protocol. International Healthcare Review (online). https://doi.org/10.56226/49.

Kim, Y.R., White, N., Braunig, J., Vijayasarathy, S., Mueller, J.F., Knox, C.L., Harden, F. A., Pacella, R., Toms, L.L., 2020. Per- and poly-fluoroalkyl substances (PFASs) in follicular fluid from women experiencing infertility in Australia. Environ. Res. 190, 109963.

Lamichhane, S., Siljander, H., Duberg, D., Honkanen, J., Virtanen, S.M., Oresic, M., Knip, M., Hyotylainen, T., 2021. Exposure to per- and polyfluoroalkyl substances associates with an altered lipid composition of breast milk. Environ. Int. 157, 106855.

Li, K., Gao, P., Xiang, P., Zhang, X., Cui, X., Ma, L.Q., 2017. Molecular mechanisms of PFOA-induced toxicity in animals and humans: implications for health risks. Environ. Int. 99, 43–54.

Li, N., Guo, M., You, S., Ji, H., 2022. On patient readiness for hospital discharge: an update on recent evidence. International Healthcare Review (online). https://doi.org/10.56226/ihr.v1i2.30.

Lim, T.C., Wang, B., Huang, J., Deng, S., Yu, G., 2011. Emission inventory for PFOS in China: review of past methodologies and suggestions. Sci. World J. 11, 1963–1980.

Liu, W., He, W., Wu, J., Wu, W., Xu, F., 2018. Distribution, partitioning and inhalation exposure of perfluoroalkyl acids (PFAAs) in urban and rural air near Lake Chaohu, China. Environ. Pollut. 243 (Pt A), 143–151.

Lloyd Williams, D., 2022. On healthcare research priorities in the USA : from long COVID to precision health, what else is new? International Healthcare Review (online) 1 (1). https://doi.org/10.56226/ihr.v1i1.14.

Lopez-Arellano, P., Lopez-Arellano, K., Luna, J., Flores, D., Jimenez-Salazar, J., Gavia, G., Teteltitla, M., Rodriguez, J.J., Dominguez, A., Casas, E., Bahena, I., Betancourt, M., Gonzalez, C., Ducolomb, Y., Bonilla, E., 2019. Perfluorooctanoic acid disrupts gap junction intercellular communication and induces reactive oxygen species formation and apoptosis in mouse ovaries. Environ. Toxicol. 34 (1), 92–98.

Lopez-Espinosa, M.J., Fletcher, T., Armstrong, B., Genser, B., Dhatariya, K., Mondal, D., Ducatman, A., Leonardi, G., 2011. Association of Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS) with age of puberty among children living near a chemical plant. Environ. Sci. Technol. 45 (19), 8160–8166.

Louis, G.M., Chen, Z., Schisterman, E.F., Kim, S., Sweeney, A.M., Sundaram, R., Lynch, C. D., Gore-Langton, R.E., Barr, D.B., 2015. Perfluorochemicals and human semen quality: the LIFE study. Environ. Health Perspect. 123 (1), 57–63.

Loureiro Pais Batista, S.M., Pereira Gaspar, A.C., Madeira dos Santos, B., da Cunha Silva, F., Fonseca Marta, F., Pinto Pedrosa, I., Lopes Martins, R.M., Sousa Albuquerque, C.M., Nunes Pereira de Azevedo e Andrade, A.I., Carvalho Duarte, J., 2023. Nurses' knowledge of patients'' swallowing ability : a cross sectional study in Portugal. International Healthcare Review (online). https://doi.org/10.56226/64.

Ma, X., Cui, L., Chen, L., Zhang, J., Zhang, X., Kang, Q., Jin, F., Ye, Y., 2021. Parental plasma concentrations of perfluoroalkyl substances and in Vitro fertilization outcomes. Environ. Pollut. 269, 116159.

Maradonna, F., Carnevali, O., 2018. Lipid metabolism alteration by endocrine disruptors in animal models: an overview. Front. Endocrinol. 9, 654, 1-14.

Marks, K.J., Howards, P.P., Smarr, M.M., Flanders, W.D., Northstone, K., Daniel, J.H., Calafat, A.M., Sjodin, A., Marcus, M., Hartman, T.J., 2021. Prenatal exposure to mixtures of persistent endocrine disrupting chemicals and early menarche in a population-based cohort of British girls. Environ. Pollut. 276, 116705.

McCoy, J.A., Bangma, J.T., Reiner, J.L., Bowden, J.A., Schnorr, J., Slowey, M., O'Leary, T., Guillette, L.J., Parrott, B.B., 2017. Associations between perfluorinated

alkyl acids in blood and ovarian follicular fluid and ovarian function in women undergoing assisted reproductive treatment. Sci. Total Environ. 605–606, 9–17.
Monachino, M., 2022. On healthcare research for disease prevention: critical knowledge gaps in European public health. International Healthcare Review (online) 1 (1). https://doi.org/10.56226/ihr.v1i1.6.
Moreira, P., 2022. On new clinical research methods and Technologies: from decentralised designs to artificial intelligence. International Healthcare Review (online) 1 (1). https://doi.org/10.56226/ihr.v1i1.11.
Nguyen, T.L.H., 2022. On improving healthcare with a world perspective: evidence for global health programs. International Healthcare Review (online) 1 (1). https://doi.org/10.56226/ihr.v1i1.10.
Niu, M., 2023. On planning and designing general hospitals in smart Technology contexts. International Healthcare Review (online). https://doi.org/10.56226/59.
Padmanabhan, V., Song, W., Puttabyatappa, M., 2021. Praegnatio perturbatio-impact of endocrine-disrupting chemicals. Endocr. Rev. 42 (3), 295–353.
Pan, C.G., Ying, G.G., Zhao, J.L., Liu, Y.S., Jiang, Y.X., Zhang, Q.Q., 2014. Spatiotemporal distribution and mass loadings of perfluoroalkyl substances in the Yangtze River of China. Sci. Total Environ. 493, 580–587.
Petro, E., D'Hollander, W., Covaci, A., Bervoets, L., Fransen, E., De Neubourg, D., De Pauw, I., Leroy, J., Jorssen, E., Bols, P., 2014. Perfluoroalkyl acid contamination of follicular fluid and its consequence for in vitro oocyte developmental competence. Sci. Total Environ. 496, 282–288.
Presunto, M., Mariana, M., Lorigo, M., Cairrao, E., 2023. The effects of bisphenol A on human male infertility: a review of current epidemiological studies. Int. J. Mol. Sci. 24 (15).
Raymer, J.H., Michael, L.C., Studabaker, W.B., Olsen, G.W., Sloan, C.S., Wilcosky, T., Walmer, D.K., 2012. Concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) and their associations with human semen quality measurements. Reprod. Toxicol. 33 (4), 419–427.
Rice, P.A., Aungst, J., Cooper, J., Bandele, O., Kabadi, S.V., 2020. Comparative analysis of the toxicological databases for 6:2 fluorotelomer alcohol (6:2 FTOH) and perfluorohexanoic acid (PFHxA). Food Chem. Toxicol. 138, 111210.
Rickard, Brittany P., Rizvi, Imran, Fenton, Suzanne E., 2022. Per- and poly-fluoroalkyl substances (PFAS) and female reproductive outcomes: PFAS elimination, endocrine-mediated effects, and disease. Toxicology 465 (2022), 153031. https://doi.org/10.1016/j.tox.2021.153031. ISSN 0300-483X.
Rosato, I., Bonato, T., Fletcher, T., Batzella, E., Canova, C., 2024. Estimation of per- and polyfluoroalkyl substances (PFAS) half-lives in human studies: a systematic review and meta-analysis. Environ. Res. 242, 117743.
Sant, K.E., Sinno, P.P., Jacobs, H.M., Timme-Laragy, A.R., 2018. Nrf2a modulates the embryonic antioxidant response to perfluorooctanesulfonic acid (PFOS) in the zebrafish, Danio rerio. Aquat. Toxicol. 198, 92–102.
Schier, A.F., 2007. The maternal-zygotic transition: death and birth of RNAs. Science 316 (5823), 406–407.
Shen, J., Kang, Q., Mao, Y., Yuan, M., Le, F., Yang, X., Xu, X., Jin, F., 2020. Urinary bisphenol A concentration is correlated with poorer oocyte retrieval and embryo implantation outcomes in patients with tubal factor infertility undergoing in vitro fertilisation. Ecotoxicol. Environ. Saf. 187, 109816.
Song, C., Xie, H., 2023. On disparities in breast cancer screening: an analysis of behavioral risk factor surveillance survey data related to racial/ethnic characteristics. International Healthcare Review (online). https://doi.org/10.56226/53.
Su, H., Lu, Y., Wang, P., Shi, Y., Li, Q., Zhou, Y., Johnson, A.C., 2016. Perfluoroalkyl acids (PFAAs) in indoor and outdoor dusts around a mega fluorochemical industrial park in China: implications for human exposure. Environ. Int. 94, 667–673.
Sun, P., Li, Z., Guo, W., Moreira, P., 2023. Evidence on the need for early identification of asymptomatic true abdominal aortic aneurysm in pregnancy: a case report. SAGE Open Medical Case Reports 11. https://doi.org/10.1177/2050313X231173789.
Sunderland, E.M., Hu, X.C., Dassuncao, C., Tokranov, A.K., Wagner, C.C., Allen, J.G., 2019. A review of the pathways of human exposure to poly- and perfluoroalkyl substances (PFASs) and present understanding of health effects. J. Expo. Sci. Environ. Epidemiol. 29 (2), 131–147.
Swift, A., Thomas, E., Larson, K., Swanson, M., Fernandez-Pineda, M., 2024. Infertility-related stress, quality of life, and reasons for fertility treatment discontinuation among US women: a secondary analysis of a cross-sectional study. Sex Reprod Healthc 39, 100955.
Taylor, K.W., Hoffman, K., Thayer, K.A., Daniels, J.L., 2014. Polyfluoroalkyl chemicals and menopause among women 20-65 years of age (NHANES). Environ. Health Perspect. 122 (2), 145–150.
Tian, M., Li, X., Zhou, F., Wang, Y., Wang, Q., Pan, N., Ji, H., 2023. On the Psychological experiences of Hematopoietic stem cell donors: an update on International Evidence. International Healthcare Review (online). https://doi.org/10.56226/31.
Tsuda, S., 2016. Differential toxicity between perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA). J. Toxicol. Sci. 41 (Special), 27–36.
Velez, M.P., Arbuckle, T.E., Fraser, W.D., 2015. Maternal exposure to perfluorinated chemicals and reduced fecundity: the MIREC study. Hum. Reprod. 30 (3), 701–709.
Wang, B., Chen, Q., Shen, L., Zhao, S., Pang, W., Zhang, J., 2016. Perfluoroalkyl and polyfluoroalkyl substances in cord blood of newborns in Shanghai, China: implications for risk assessment. Environ. Int. 97, 7–14.
Wang, B., Zhang, R., Jin, F., Lou, H., Mao, Y., Zhu, W., Zhou, W., Zhang, P., Zhang, J., 2017. Perfluoroalkyl substances and endometriosis-related infertility in Chinese women. Environ. Int. 102, 207–212.
Wang, Y., Wang, L., Chang, W., Zhang, Y., Zhang, Y., Liu, W., 2019a. Neurotoxic effects of perfluoroalkyl acids: neurobehavioral deficit and its molecular mechanism. Toxicol. Lett. 305, 65–72.
Wang, Y., Wang, L., Chang, W., Zhang, Y., Zhang, Y., Liu, W., 2019b. Neurotoxic effects of perfluoroalkyl acids: neurobehavioral deficit and its molecular mechanism. Toxicol. Lett. 305, 65–72.
Wang, M., Yang, Q., Chen, Y., 2024. International comparison of the financing mechanism of basic medical insurance and its implications for China. International Healthcare Review (online). https://doi.org/10.56226/63.
Wei, Y., 2023. Opportunities and challenges in cross-border healthcare: a case study based on the Court of Justice of the European Union. International Healthcare Review (online). https://doi.org/10.56226/65.
Wei, L., Xue, J., 2022. A longitudinal study on the emotional support mechanism of the mental health of empty nesters: recent evidence from China national health and retirement survey. International Healthcare Review (online). https://doi.org/10.56226/37.
WHO, 2023. Infertility Prevalence Estimates, 1990–2021. World Health Organization, Geneva, 2023. Licence: CC BY-NC-SA 3.0 IGO.
Wolf, C.J., Schmid, J.E., Lau, C., Abbott, B.D., 2012. Activation of mouse and human peroxisome proliferator-activated receptor-alpha (PPARalpha) by perfluoroalkyl acids (PFAAs): further investigation of C4-C12 compounds. Reprod. Toxicol. 33 (4), 546–551.
Xiao, S., Diao, H., Smith, M.A., Song, X., Ye, X., 2011. Preimplantation exposure to bisphenol A (BPA) affects embryo transport, preimplantation embryo development, and uterine receptivity in mice. Reprod. Toxicol. 32 (4), 434–441.
Xie, X., Weng, X., Liu, S., et al., 2021. Perfluoroalkyl and polyfluoroalkyl substance exposure and association with sex hormone concentrations: results from the NHANES 2015–2016. Environ. Sci. Eur. 33, 69. https://doi.org/10.1186/s12302-021-00508-9.
Zeng, X.W., Bloom, M.S., Wei, F., Liu, L., Qin, J., Xue, L., Wang, S., Huang, G., Teng, M., He, B., Mao, X., Chu, C., Lin, S., Dong, G.H., Tan, W., 2023a. Perfluoroalkyl acids in follicular fluid and embryo quality during IVF: a prospective IVF cohort in China. Environ. Health Perspect. 131 (2), 27002.
Zeng, X.W., Bloom, M.S., Wei, F., Liu, L., Qin, J., Xue, L., Wang, S., Huang, G., Teng, M., He, B., Mao, X., Chu, C., Lin, S., Dong, G.H., Tan, W., 2023b. Perfluoroalkyl acids in follicular fluid and embryo quality during IVF: a prospective IVF cohort in China. Environ. Health Perspect. 131 (2), 27002.
Zhang, S., Tan, R., Pan, R., Xiong, J., Tian, Y., Wu, J., Chen, L., 2018. Association of perfluoroalkyl and polyfluoroalkyl substances with premature ovarian insufficiency in Chinese women. J. Clin. Endocrinol. Metab. 103 (7), 2543–2551.
Zhang, Y., Xu, Y., Ding, H., Yu, W., Chen, L., 2021. Prenatal exposure of female mice to per fl uorononanoic acid delays pubertal activation of the reproductive endocrine axis through enhanced hepatic FGF21 production. Chemosphere 269, 128776.
Zhang, L., Lei, J., Zhang, J., et al., 2022a. Undiagnosed long COVID-19 in China among non-vaccinated individuals: identifying persistent symptoms and impacts on patients' health-related quality of life. J Epidemiol Glob Health. https://doi.org/10.1007/s44197-022-00079-9.
Zhang, L., Moreira, J.P., Xi, Y., 2022b. What is long COVID-19? Clarifying definitions and symptoms. International Healthcare Review (online). https://doi.org/10.56226/ihr.v1i2.28.
Zhang, Yujiao, Zhang, Yong, Ren, Manyi, Xue, Minghua, Hu, Chunying, Hou, Yinglong, Li, Zhiyuan, Qu, Haiyan, Moreira, Paulo, 2023a. Atrial standstill associated with lamin A/C mutation: a case report. SAGE Open Medical Case Reports 2023, 11. https://doi.org/10.1177/2050313X231179810.
Zhang, B., Li, Y., Cao, M., Xu, C., 2023b. On Workplace bullying in nursing: findings from a rapid review of the literature. International Healthcare Review (online). https://doi.org/10.56226/51.
Zhou, W., Zhang, L., Tong, C., Fang, F., Zhao, S., Tian, Y., Tao, Y., Zhang, J., 2017. Plasma perfluoroalkyl and polyfluoroalkyl substances concentration and menstrual cycle characteristics in preconception women. Environ. Health Perspect. 125 (6), 067012.
Zhou, Z., Zheng, D., Wu, H., Li, R., Xu, S., Kang, Y., Cao, Y., Chen, X., Zhu, Y., Xu, S., Chen, Z.J., Mol, B.W., Qiao, J., 2018. Epidemiology of infertility in China: a population-based study. BJOG 125 (4), 432–441.
Zhou, Y., Li, H., Lin, C., Mao, Y., Rao, J., Lou, Y., Yang, X., Xu, X., Jin, F., 2020. Perfluorooctanoic acid (PFOA) inhibits the gap junction intercellular communication and induces apoptosis in human ovarian granulosa cells. Reprod. Toxicol. 98, 125–133.

Update

Environmental Research

Volume 266, Issue , 1 February 2025, Page

DOI: https://doi.org/10.1016/j.envres.2024.120696

Environmental Research 266 (2025) 120696

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Corrigendum to 'Exposure of women undergoing in-vitro fertilization to per-and polyfluoroalkyl substances: Evidence on negative effects on fertilization and high-quality embryos' [Environ. Pollut. **359** (2024) 124474]

Juan Shen [a], Yuchan Mao [b], Hongyan Zhang [c], Hangying Lou [a], Ling Zhang [a], Joaquim Paulo Moreira [d,e,f,*], Fan Jin [b]

[a] *Center for Reproductive Medicine, Department of Reproductive Endocrinology, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou, Zhejiang, China*
[b] *Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, China*
[c] *Hangzhou Women's Hospital, 369 Kunpeng Road, Hangzhou, China*
[d] *International Healthcare Management Research and Development Center (IHM_RDC), The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Shandong, Jinan, China*
[e] *Henan Normal University, School of Social Affairs, Xinxiang, China*
[f] *Atlantica Instituto Universitario, Gestao em Saude, Oeiras, Portugal*

The authors regret that there was a mistake in the attribution of Affiliations of Authors in the published version. The affiliations of all the authors are correct in this Corrigendum for all applicable purposes.

The authors would like to apologize for any inconvenience caused.

DOI of original article: https://doi.org/10.1016/j.envpol.2024.124474.

* Corresponding author. International Healthcare Management Research and Development Center (IHM_RDC), The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Shandong, Jinan, China.
E-mail address: jpm2030@outlook.com (J.P. Moreira).

https://doi.org/10.1016/j.envres.2024.120696

Available online 2 January 2025