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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

A.L. Heffernan[a,b,1], T.K. Cunningham[c,d,1], D.S. Drage[a,e], L.L. Aylward[a,f], K. Thompson[a], S. Vijayasarathy[a], J.F. Mueller[a], S.L. Atkin[g], T. Sathyapalan[c,*]

[a] Queensland Alliance for Environmental Health Sciences, The University of Queensland, Australia
[b] Melbourne Dementia Research Centre, The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Australia
[c] Centre for Cardiovascular and Metabolic Research, Hull York Medical School, University of Hull, UK
[d] The Hull IVF Unit, Women's and Childrens' Hospital, Hull Royal Infirmary, Hull, UK
[e] School of Geography, Earth and Environmental Sciences, University of Birmingham, UK
[f] Summit Toxicology, LLP, USA
[g] Weill Cornell Medicine Qatar, Education City, Qatar Foundation, Doha, Qatar

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ABSTRACT

Women with polycystic ovarian syndrome (PCOS) undergoing treatment for infertility could be a sensitive subpopulation for endocrine effects of exposure to perfluorinated alkyl acids (PFAAs), persistent organic pollutants with potential endocrine activity. Women with, PCOS (n = 30) and age- and BMI-matched controls (n = 29) were recruited from a UK fertility clinic in 2015. Paired serum and follicular fluid samples were collected and analysed for 13 PFAAs. Sex steroid and thyroid hormones, and metabolic markers were measured and assessed for associations with serum PFAAs. Four PFAAs were detected in all serum and follicular fluid samples and concentrations in the two matrices were highly correlated ($R^2 > 0.95$): perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonate (PFHxS), and perfluorononanoic acid (PFNA). Serum PFOS was positively associated with age (1 ng/mL per yr, $p < 0.05$) and was higher in PCOS cases than controls (geometric mean [GM] 3.9 vs. 3.1 ng/mL, $p < 0.05$) and in women with irregular vs. regular menstrual cycles (GM 3.9 vs. 3.0 ng/mL, $p = 0.01$). After adjustment for confounders, serum testosterone was significantly associated with PFOA, PFHxS, PFNA, and the molar sum of the four frequently detected serum PFAAs (approximately 50 percent increase per ln-unit) among controls but not PCOS cases. HbA1c in PCOS cases was inversely associated with serum PFOA, PFHxs, and sum of PFAAs (2–3 mmol/mol per ln-unit). In controls, fasting glucose was positively associated with serum PFOA and sum of PFAAs (0.25 nmol/L per ln-unit increase in PFAAs). Few other associations were observed. The analyses and findings here should be considered exploratory in light of the relatively small sample sizes and large number of statistical comparisons conducted. However, the data do not suggest increased sensitivity to potential endocrine effects of PFAAs in PCOS patients.

1. Introduction

Perfluorinated alkyl acids (PFAAs; perfluorinated chemicals (PFCs)) consist of a fluorinated hydrophobic alkyl chain with a hydrophilic end group, and are used widely as surfactants in household and industrial applications such as textile treatments, food packaging, and as aqueous film-forming foams. The dominant exposure pathway for humans is diet, particularly meat and fish, and via breast milk for infants (Gebbink et al., 2015; Haug et al., 2010; Kärrman et al., 2007). PFAAs are persistent and bioaccumulative. Elimination of PFAAs depends on chain length and they sequester particularly in the liver and kidney. They are non-covalently bound to protein in serum, particularly serum albumin (Andersen et al., 2008; Bischel et al., 2010). Serum elimination half-life is approximately 3.8 and 5.4 years for perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA), respectively (Li et al., 2018; Olsen et al., 2007). PFAAs can cross the placenta (Kim et al., 2011), and have

* Corresponding author. Michael White Diabetes Centre, Hull Royal Infirmary, Hull, HU3 2RW, UK.
E-mail address: thozhukat.sathyapalan@hyms.ac.uk (T. Sathyapalan).
[1] Joint first authors.

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Table 1
Summary of PFAA serum concentrations in PCOS case-control study (ng/mL).

	Detection frequency, n (%)		Geometric Mean		Range		Average ratio	LOR	
	Serum	FF	Serum	FF	Serum	FF	FF:Serum	Serum	FF
PFOS	59 (100)	58 (100)	3.46	2.00	0.93–7.71	0.60–4.29	0.59	0.5	0.2
PFOA	59 (100)	58 (100)	2.39	1.82	0.5–8.16	0.43–6.64	0.78	0.1	0.1
PFHxS	59 (100)	58 (100)	1.04	0.88	0.2–10.2	0.1–9.07	0.86	0.05	0.1
PFNA	59 (100)	58 (100)	0.57	0.41	0.2–1.79	0.1–1.43	0.77	0.2	0.1
PFDA	45 (76)	14 (24)	0.31	–	< LOR-1.17	< LOR-0.87	–	0.2	0.2
PFPeA	29 (49)	0	–	–	< LOR-2.02	–	–	0.5	0.3
PFUnDA	21 (36)	0	–	–	< LOR-0.47	–	–	0.2	0.7
PFHpA	10 (17)	9 (15)	–	–	< LOR-0.70	< LOR-0.53	–	0.1	0.1
PFBS	4 (6.8)	12 (21)	–	–	< LOR-0.46	< LOR-0.44	–	0.2	0.2
PFBA	0	0	–	–	–	–	–	0.5	0.2
PFHxA	0	0	–	–	–	–	–	0.5	0.1
PFDS	0	0	–	–	–	–	–	0.5	0.1
PFDoDA	0	0	–	–	–	–	–	0.5	0.4

FF, follicular fluid; LOR, limit of reporting; PFOS, perfluorooctane sulfonate; PFOA, perfluorooctanoic acid; PFHxS, perfluorohexane sulfonate; PFNA, perfluorononanoic acid; PFDA, perfluorodecanoic acid; PFPeA, perfluoropentanoic acid; PFUnDA, perfluoroundecanoic acid; PFHpA, perfluoroheptanoic acid; PFBS, perfluorobutanesulfonate; PFBA, perfluorobutanoic acid; PFHxA, perfluorohexanoic acid; PFDS, Perfluorodecane sulfonate; PFDoDA, perfluorododecanoic acid.

been associated with adverse effects on fertility, birth outcomes, and early development in humans (Bach et al., 2015; Goudarzi et al., 2016; Lyngso et al., 2014; Olsen et al., 2009). PFOS and PFOA have intrinsic estrogenic activity and anti-estrogenic effects *in vitro* (Henry and Fair, 2013), and PFOS is capable of modulating steroidogenesis (Kraugerud et al., 2011). *In vivo*, PFAAs were associated with increased breast cancer risk in Inuit women, perhaps related to their estrogenic effects (Bonefeld-Jorgensen et al., 2011), while other studies have shown increased serum PFAAs associated with an earlier menopause, and with PFOS being inversely associated with estradiol levels (Knox et al., 2011). Because PFAAs are eliminated via both menstruation and renal elimination, it may be difficult to assess and interpret relationships between serum PFAA concentrations and outcomes such as birth weight, which can be affected by glomerular filtration rates, or timing of menopause, which can influence PFAA levels due to decreased elimination of PFAAs post-menopause (Ruark et al., 2017; Verner et al., 2015).

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders and affects 6–20% of reproductive-aged women (Bozdag et al., 2016; March et al., 2010; Teede et al., 2013; Yildiz et al., 2012) with clinical manifestations of irregular menstruation, hyperandrogenism and/or polycystic ovaries (Bozdag et al., 2016; PCOS Consensus Workshop, 2004). PCOS is associated with infertility, hirsutism, and acne (Ehrmann, 2005; Norman et al., 2007). Thus, PCOS patients may be a sensitive subpopulation for compounds that alter endocrine outcomes. The previously reported association of PFAAs with menstrual irregularity and infertility (Lyngso et al., 2014; Velez et al., 2015) may have been influenced by the inclusion of women with PCOS in the studies. The aim of the study was to examine correlation of serum and follicular fluid measures of PFAAs, and to explore the associations of PFAAs with hormonal parameters in women with and without PCOS, and undergoing fertility treatment.

2. Materials and methods

This prospective cohort study was performed within the Hull IVF Unit, UK following approval by The Yorkshire and The Humber NRES ethical committee, UK (approval number 02/03/043). The PCOS subjects were recruited sequentially in 2015, using the revised 2003 criteria from the Rotterdam ESHRE/ASRM sponsored PCOS consensus workshop group, indicating PCOS to be present if any 2 out of 3 criteria were met: menstrual disturbance (oligo or amenorrhoea), clinical and/or biochemical signs of androgenism or polycystic ovaries on ultrasound (PCOS Consensus Workshop, 2004). Inclusion criteria were age 20–45 years, BMI ≤35 and undergoing *in vitro* fertilisation. Patients with known immunological disease, diabetes, renal or liver insufficiency, acute or chronic infections, or inflammatory diseases were excluded from the study. No comparative study on which to base formal power calculations was available; therefore, power and sample size for pilot studies has been reviewed (Birkett and Day, 1994) that concluded that a minimum of 20 degrees-of-freedom was required to estimate effect size and variability. Hence, we planned to recruit 25 patients per group with an additional 5 patients allowing for drop-outs and covariate adjustment. A total of 59 women were recruited into the study, 30 PCOS cases and 29 control subjects matched for age and weight.

2.1. Sample collection

The subjects fasted from midnight and had a fasting blood sample taken on day 21 of the luteal phase of the cycle before commencing their IVF treatment. Follicular fluid samples were collected during ovum retrieval on the second visit, for which patients also fasted. Fasting venous blood samples were collected, separated by centrifugation at 3500 × g for 15 min at 4 °C, and the aliquots stored at −80°oC within 1 h of collection. Plasma glucose was measured using a Synchron LX20 analyzer (Beckman-Coulter), and serum insulin was assayed using a competitive chemiluminescent immunoassay performed using the DPC Immulite 2000 analyzer (Euro/DPC, Llanberis, UK). mLC reactive protein (CRP) was measured enzymatically using a Synchron LX20 analyzer (Beckman-Coulter, UK). Estradiol and all thyroid assays were performed on an Abbott Architect i4000 immunoassay analyzer (Abbott Diagnostics Division, UK). Serum testosterone and androstenedione were measured by liquid chromatography tandem mass spectrometry (LC/MS/MS; Acquity UPLC-Quattro Premier XE-MS, Waters, Manchester, UK). Sex hormone binding globulin (SHBG) was measured by an immunometric assay with fluorescence detection (DPC Immulite 2000 analyzer; upper limit 2.0 nmol/l). Glycosylated hemoglobin A1c (HbA1c) measurements were made using ion-exchange chromatography.

2.2. Analysis for PFAAs

Samples were analysed for 13 PFAAs including PFOS, PFOA, perfluorohexane sulfonate (PFHxS), perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDA) (Table 1). 200 µL serum or follicular fluid was transferred to a 2 mL Eppendorf tube, followed by addition of the internal standards. Proteins were precipitated with acetonitrile, centrifuged, filtered (2 µm GHP membrane; Pall, East Hills, NY, USA), and concentrated under gentle stream of nitrogen. Samples were reconstituted in 5 mM ammonium acetate in water prior to analysis via

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