PFAS Exposure and Ovarian Function

Summary by : Tia Mohanani
Date : August 2021
Professor : Caryl Waggett

About the Student: Tia Mohanani is a student at Jayshree Periwal International School, India. This paper was prepared by Tia as a part of her course work for LS190 - Introduction to College Level Research course at Allegheny College during summer 2022.

Abstract

Deemed 'forever chemicals' that are environmentally persistent, PFAS (Per- and poly-fluoroalkyl substances) have increased consumption and its adverse and widespread effects are only getting worse. For decades, PFAS has been used in almost every walk of life like home, food, storage, and personal care, which is what makes its exposure and thus its negative effects very high. There are many sources of exposure, one of them being the water supplies in countries around the world. This 'contaminated' water has been repeatedly associated with various health outcomes in humans. PFAS act as endocrine disruptors as they interfere with a woman's reproductive system, specifically the ovary, which may cause great damage to a woman's health. The role of these PFAS affecting the female reproductive system, the main target being the organ, will be the focus of this review. By doing a thorough review of articles via PubMed and Google Scholar, with various search terms like PFA'S, ovarian disorders, endocrine disruptors, ovaries, reproductive system. These were then narrowed down to specific search terms like steroid hormones, menarche, menopause, and ovary and PFA exposure). The literature review suggests that PFAS exposure and presence in follicles are harmful to women. Not only are they found in this follicular fluid but can also pass the blood–follicle barrier. While various studies deemed no results linking PFAS exposure with ovarian disruption, various cross-sectional designed studies had a strong correlation between PFAS and disorders that are a result of ovarian disorders such as early menopause, later menarche, and irregular menstrual cycles, and longer cycle length. Zooming in to the molecular level, various studies have shown have PFAS could diminish ovarian reserve and reduce endogenous hormone synthesis through activating peroxisome proliferator-activated receptors, disrupting gap junction intercellular communication between oocyte and granulosa cells, and inducing thyroid hormone deficiency. The literature published shows a strong correlation between PFAS exposure and ovarian disorders however the evidence is still limited to portraying a cause and effect relationship between the two. Thus, more research on the topic needs to be conducted. The environmental exposure aspect of the disease isn't considered when looking at reproductive disorders by the medical community. Thus, to fully comprehend the potential risks of PFAS on ovarian function, investigations need to be carried out.

Keywords: Female reproduction, Perfluoroalkyl and Polyfluoroalkyl substances (PFAS), Endocrine-disrupting Chemicals (EDCs), Ovaries, Environmental Contaminants, Folliculogenesis,

Introduction

Endocrine-disrupting chemicals (EDCs) are chemicals that mimic or interfere with the hormones in the body's endocrine system. They are either artificial or manmade and via environmental or inappropriate developmental exposures, alter the hormonal and homeostatic systems that enable the organism to communicate with and respond to its environment (Diamanti-Kandarakis et al., 2009). Various day-to-day use chemicals in the industrial environment are considered endocrine disturbing: lubricants such as polychlorinated biphenyls, flame retardants such as polybrominated diethyl ethers, and pesticides such as dichlorodiphenyltrichloroethane and chlorpyrifos (Burger et al., 2007). Among these environmental contaminants, perfluoroalkyl and polyfluoroalkyl substances (PFAS) have been getting much more attention as they have been found in increased amounts in drinking water, which is impacting over 10 million citizens of the United States of America. (Environmental Working Group, 2018) PFAS are highly stable florunien carbon bonded

artificial chemicals that can be categorized as environmental toxicants and their widespread nature has caused nearly every person sampled for their blood, to be exposed to it (CDC, 2019). Textile, food storage, non-stick cookware, flame and water-resistant clothing, furniture, and cosmetics are just a few examples of their vast use in the populations day to day interactions (Bradley et al., 2007.) Their most prominent source of exposure is, however, through the drinking water (specifically in the USA). They can be found in the water present near industrial sites, fire-fighting facilities, and military installations. While many regulatory bodies and the government are trying to stop the extensive usage of these PFAS to limit their adverse effects globally, companies have just shifted their focus on its alternative chemicals (Ateia et al., 2019). This raises a concern and calls attention to the urgent need to raise awareness about the harmful effects of PFAS on human health, specifically its toxicity to the reproductive system (Jensen and Leffers, 2008). According to Lopez-Espinosa et al. (2011), exposure to PFAS could delay menarche. This along with other studies like Zhou et al. (2017), Taylor et al.(2014), Zhang et al. (2018) and Barrett et al. (2015) show how PFAS exposure could also result in menstrual cycle irregularity, early menopause, premature ovarian insufficiency and altering levels of circulating sex steroid hormones respectively.

Folliculogenesis is a key process that cannot take place without proper functioning of the ovary, and thus an ovarian disorder could cause depletion of ovarian reserve (Bellingham et al., 2009). When this process and network are disrupted, the physiologic impacts might affect not only the reproductive system of a woman's body but also her overall health. Ovaries have been a potential target for PFAS toxicity, and the lack of a comprehensive review regarding its effects has been a gap in the research of today. Thus, the review of this focus would be on the sources and pathways of PFAS, as well as the state of the science regarding associations between PFAS exposures and ovarian disorders in varying study types. An outline for the possible future research questions is also highlighted in this review.

Methods

The goal of this paper was to identify the role of PFAS affecting the female reproductive system, specifically the ovaries. Sources for this review were sound using the following search terms: PFAS, polyfluoroalkyl, perfluorinated, fluorocarbons, perfluorobutanoic acid, perfluorooctanoic acid, perfluorooctanoic acid, perfluorooctanoic acid, perfluorooctanoic acid, PFASs and water, PFAS in women, PFAS reproductive system, ovary, follicle, oocyte, menstrual cycle, menopause, primary ovarian insufficiency, menarche, and ovarian disruption in several databases. These included PubMed, National Center for Biotechnology, ScienceDirect, and ERIC. The review focused on articles from 2019 to 2022. All searches were also limited to full text that was available in English.

PFAS and its exposure

PFAS are perfluoroalkyl and polyfluoroalkyl substances and can be referred to as artificial chemicals that are highly stable. They have a distinct chain of carbon atoms that are bonded to fluorine atoms, giving them a stable structure. This bond is extremely strong and thus these chemicals are environmentally persistent. They are highly resistant to complete degradation. The basic chemical structure can be written as $C_nF_{2n+1} - R$, in which the 'C_nF_{2n+1}' defines the length of the perfluoroalkyl chain tail and the 'R' refers to the attached functional group. This can differ for the various types of chemicals present: if a 'COOH' group is attached, it becomes a PFCA; if a 'SO_3H' group is attached, it becomes a PFSA, and so on. The most common type of PFA molecules is Perfluoroalkyl acids (PFAAs) which are also non-degradable. They contain three major groups that differ only from their end functional group: perfluoroalkyl carboxylic acids (PFCAs), perfluoroalkyl sulfonic acids (PFSAs) and perfluoroalkyl phosphonates (PFPAs). Small PFAS monomer molecules can also join together to form PFAS polymers. A study conducted also revealed that while some basic polymers may be broken down, non-polymer PFAS are not degradable.

PFAS exposure

Due to its vast nature, PFAS exposure is extremely high in our daily lives. (Fromme et al., 2007) PFAS serum concentrations the world are extremely high worldwide, but due to differences like age, sex, and geographical locations, they cannot be compared. Multiple studies like Tittlemier et al. (2007), Post et al. (2009), Piekarz et al. (2007), and Begley et al. (2005), all reveal the various sources of exposure which include one's diet, drinking water, air and dust and

consumer products respectively. One more reason for their vast nature is the fact that they are improperly disposed of and due to this, their degradation resistance has led to humans inhaling them or eating them. Different sources of PFAS and the way they reach the human body are highlighted in Table 1.

Table 1: Human Exposure to sources and their route

Sources	**Routes**
Fish and Shellfish, Drinking Water, Food Packaging materials, Non-Stick cookware, Dairy Products, Eggs, Beverages	Ingestion
Indoor air and dust	Inhalation
Soil and sediment	Environmental
Cosmetics, Furniture Spray, Skin Wax	Dermal Absorption

As it can be observed from the table, the main source of exposure is through ingestion, particularly to PFOS and PFOA (Tittlemier et al., 2007) Due to their vast usage in the seafood industry, fish and shellfish are usually the ones with the highest PFAS concentration (Domingo and Nadal, 2017) Dietary sources such as eggs and vegetables ((Haug et al., 2010) have a lower concentration and detection compared to fish and shellfish (Jian et al., 2017) Food packaging (Schaider et al., 2017), non-stick cookware (Begley et al., 2005), drinking water (Domingo and Nadal, 2019) are also various places where PFAS exposure is found to be highest. Various studies like Takagi et al., 2008; Jin et al., 2009; Mak et al., 2009; Quinte et al., 2009; Quiñones and Snyder, 2009; Wilhelm et al. 2010, also measured the PFAS concentrations in various countries. One specific study that was conducted recently was Boone et al. (2019) which tested the PFAS levels in water for 24 states across the US. Out of the 24, 17 samples conducted high levels of PFAS ranging from 1–1102 ng/L (which exceeds the health advisory limit of 70 ng/L set by the United States Environmental Protection Agency). Another study by Kubwabo et al. 2005, also searched for PFA levels in 67 houses in Canada. The results revealed that the carpeted homes had higher concentrations of PFOS in the dust. According to Kotthoff et al., 2015, products such as ski waxes, outdoor textiles, leather samples, and cosmetics products also contain PFAS. A recent study by Vestergren and Cousins, 2009, also predicted that the largest source of exposure to PFOA is found to be oral ingestion and drinking water.

Pathways of PFAS

While environmentally persistent molecules like polychlorinated biphenyls (PCBs) are lipophilic, the reason why PFAS are the strongest of them all is due to their carbon-fluorine bond and its highly charged functional group ‘R,’ which makes them not only hydrophobic but lipophobic as well. (Banks and Tatlow, 1994). PFAAs are one type of endocrine disrupting chemicals that instead of being stored in the adipose tissue undergoing extensive enterohepatic circulation like other EDCs, are stored in the liver and serum instead (Pérez et al. 2013) Since this EDC is also hydrophobic in nature, it contains a fluorine-containing compound that leads to increased affinity in proteins, which gives them a very high protein density in the tissue to up to 99% when consumed (Jones et al., 2003). According to the study by Petro et al. 2014, since PFAAs can pass through the blood follicle barrier, they are easily transported to growing follicles which is why they have been detected in human follicular fluid. This could not only alter oocyte maturation but also damage or cause the follicle development in vivo to be at a halt. According to Han et al (2008) the primary elimination pathway for a PFAA is through urine. Other pathways of elimination include menstruation (according to Wong et al (2014) it was found that 30% of the PFOS elimination half-life difference between females and males is attributable to menstruation), pregnancy (Monroy et al., 2008) and lactation (Bjermo et al., 2013). A major factor in determining the renal clearance of PFAAs is sex hormones. According to the study of Kudo et al. (2002), in ovariectomised female rats, oestradiol could facilitate the transport of PFAAs across the membranes of kidney tubules into the glomerular filtrate, resulting in lower serum

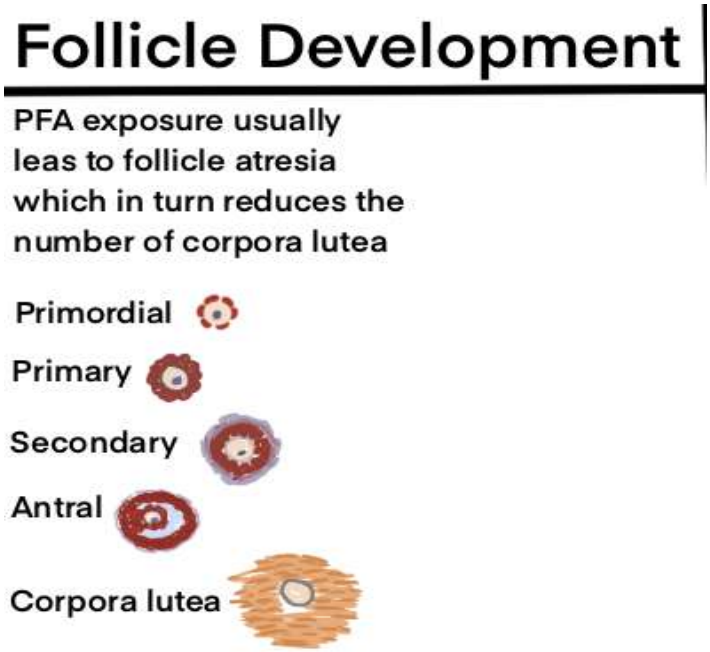
concentrations (Serum concentrations of PFOA, PFOS, PFHxS and PFNA appear to be higher in males than in females across all age groups (Calafat et al., 2007). One important study by Dhingra et al., 2017, also showed how the differences by sex in PFAAs levels reduce with ageing, showing that they might reaccumulate after menopause. Despite various challenges like sampling time intervals, duration of exposure, sex and age of study subjects, studies mentioned above could report that the half-life in humans of PFOA is around 3 years and that of PFOS is 5 years.

Toxicity in the Ovaries: Introduction

Folliculogenesis disruption

An important endocrine organ of a woman's body is her ovary. They consist of an outer cortex, an epithelial surface and as we go further down, a dense connective tissue (tunica albuginea), and an inner medulla. The medullas have several blood vessels, lymphatic vessels and nerves, making them extremely vascular. The other elements that the ovary consists of are the ovarian follicles, the corpus luteum and the stroma. This is also a reason for their dense and granular appearance. An ovary has various functions in a woman's body: It releases the female gamete and is responsible for its production and maturation. Furthermore, it has to manage the synthesis of the female sex steroid hormone that regulates reproductive function. According to Vabre et al. (2017), environmental exposure to PFAS usually depletes the follicular cells and empties the oocytes which are the main causes of menopause at an earlier age, infertility and premature ovarian failure. The effects of PFA exposure via diagram on follicle development are highlighted in the diagram below.

Figure 1



Oogenesis disruption

The reason for the disruption in the folliculogenesis stage of a woman's health is due to the disruption caused in the oocyte development (Domínguez et al., 2016). Peroxisome proliferator-activated receptors (PPARs) are hormone receptors that are a major reason for PFAS-induced reproductive stress (Desvergne and Wahli, 1999). According to Komar et al (2001), there are three types of PPARs, α, β/δ and γ, and they all play a key role in the ovary: PPAR-α and PPAR-β/δ isoforms show expression in the stromal cells in the ovary (PPAR-α's are the main reason PFAS can intersect with PPAR's in the first place, causing metabolic disturbances) where whereas PPAR-γ isoform is found in granulosa cells and the corpus lutea. According to Komar 2005, it also causes the expression of the meiosis cells to be inhibited,

which are key genes in femulate gumtree development. The ovary destruction is done by activating the peroxisome proliferator-activated receptor (PPAR) signalling pathways and disrupting the intercellular communication between oocytes and granulosa cells and induction of oxidative stress. One study that supports this hypothesis is Prates et al. 2014. The results of the study revealed that excessive lipids in the ooplasm correlated with impaired oocyte developmental competence and low oocyte survival rates because PFAS can bind and activate PPARs and play an important role in PPAR signalling during ovarian follicle maturation and ovulation. This consistent activation of ovarian systems and exposure to PFAS may disrupt the ovarian cell function and oocyte maturation completely. According to Clark et al. (2018), apart from PPAR signalling activation, PFAS exposure could also disrupt follicle cell-to-cell communication. This was found by the study experiment that was as follows: An aqueous solution with 0, 12.5, 25 and 59 μM PFOS in vitro for a 44-h maturation period, the number of live oocytes and the percentage of matured oocytes decreased in porcine ovaries (Domínguez et al., 2016). These results are due to an inhibition of a gap junction between the intercellular communication between oocytes and granulosa cells (Domínguez et al 2016) One more harm of PFA's is that they cause oxidative stress with a very high reactive oxygen species (ROS) value which not only increases DNA damage but also decreases total antioxidant capacity (Wielsøe et al., 2015). Another study reported significantly increased ROS production in rats exposed to PFOA, which interfered with the activities of complexes I, II and III in the mitochondrial respiratory chain.

Follicle development disruption

At several stages of development of the ovarian follicular cell, PFAS are seen altering or disrupting its phases. Various rodent studies have proven this hypothesis. According to Feng et al., 2015, when female mice were exposed to 0.1 mg of PFOS every day for 4 months, the number of preovulatory follicles decreased and the atretic follicles increased. Secondly, the PFOS-exposed mice have reduced oestradiol serum and progesterone serum levels. PFOS found not only did the following but also decreased the extent to which mRNA expression occurs in a steroidogenic acute regulatory protein (Star), which codes for the StAR protein that transports cholesterol from the outer to the inner mitochondrial membrane, a critical step in steroid hormone biosynthesis. One similar study was conducted by Chen et al., 2017, where they exposed pregnant mice to 2.5, 5 and 10 mg PFOA/kg/day from gestational days 1–7 or 1–13. This resulted in a decreased number of corpora lutea accompanied by decreased mRNA expression of Star in the maternal ovaries. Furthermore, according to Du et al (2019), when female rats were exposed to 0.1 and 1 mg PFOA per day, there was a decrease in the number of ovarian primordial follicles, growing follicles and corpora lutea. One more aspect that Du et al. brings bring in is the KiSS1 metastasis-suppressor (Kiss1). Since signalling of kisspeptin has an important role in the process of the ovarian cycle as well as initiation of puberty, the PFOA and PFOS follicular development perturbation may have resulted from these signalling disruptions in the hypothalamus (Bellingham et al., 2009). Another study that supports the negative effects of PFAS on ovaries is Feng et al. (2017). In it, there were oral doses of 200- 500 mg of perfluoro butane sulfonate (PFBS) given for 20 days (the period of gestation.) The results revealed that the female offspring had not one but various symptoms of a destructed ovary from the decreased number of ovarian follicles and depressed ovarian size and weight, to opening, delayed onset of oestrus and prolonged diestrus and reduced serum levels of oestradiol. Another important aspect of this disturbance in ovary function is the decrease in hormone levels of the thyroid. According to Wakim et al. (1994), thyroid hormones do contribute to follicular ovary maturation, development and maintenance of other physiological functions. It thus may be possible that a decrease in these thyroid hormones may have adverse effects on follicle development. These adverse effects may be caused by attacking the follicular fluid inhibin and other cytokines (Dijkstra et al., 1996)

Toxicity In The Ovaries: Outcomes

As mentioned and supported by the studies above, ovarian folliculogenesis is an essential process for normal reproductive health. If it was disrupted by PFAS it could have various negative effects. Exposure to PFOA causes the delay of menarche, ovarian ageing various other conditions that may take a human's life such as ovarian cancer.

Delayed Menarche

According to Palmert and Dunkel (2012), delayed menarche can be classified as the lack of visible signs of puberty by the age of 13. In the long run, the meantime that occurs late might cause cardiovascular disease once a human being turns into an adult as per Zhu and Chan (2017). Various previous studies such as Christensen et al 2011. don't align with the hypothesis that exposure to PFAs delays the menarche process. In it, researchers tested girls with age of menarche (8-13) before and after 12.5 years and the results revealed that from 218 cases and 230 controls, median maternal PFOA and PFOS exposure was 3.7% and 19.8% respectively. The outcome of this is the fact that early menarche occurred and thus no association between exposure and menarche was established. However, in the case of Lopez-Espinosa et al (2011), when 293 girls between the ages of 8–18 years were tested, elements and serum concentrations of PFOA and FOS serums were high (28.2% and 20.2% respectively). The higher the serum concentration, the more delayed the menarche is. With PFOA it was 130 days while with PFOS it was 138 days. Another study that can be used to support the thesis is Kristensen et al., 2013. In it, 267 female offspring that were young (1988) were followed up 20 years later (2008), and it was revealed that women with in utero exposure to higher concentrations of PFOA reached menarche 5.3 months later compared with the reference group of lower PFOA concentrations. While this study revealed this association for PFOA, there was no link established between PFOS and delayed menarche, which is why for a stronger conclusion, more studies need to be conducted.

Menstrual Cycle

The main features of a menstrual cycle should be the fact that they are regular have a normal (5-6 days) cycle length and the have correct amount of flow, While these factors vary in every woman - 3 to 6 days and heavy to light flow- the number of studies that still support the thesis that PFAS exposure on a woman's reproductive system is harmful is significantly high. In Fei (2009)’s cross-sectional study, the sample size consisted of 1240 participants (mean age 30.6) and the median exposure to PFOA and PFOS was 5.3% and 33.7% respectively. They were told to self-report their irregular menses and the results revealed that for PFOAs the proportion of women in the lowest was 9.0% and the highest quartiles were 15.0%. For PFOS, it was 111.6% and 14.2% respectively. In Zhou et al (2017), 950 pregnant/ attempting to get pregnant, women from the ages of 28-32 were taken. The median PFOA and PFOS exposure were 13.8 and 10.5% respectively. The results revealed that when considering longer and irregular cycles, PFOA increased 2.0% for both respectively (longer cycle length is > 31 days and irregular cycles were considered to have more than 7 days gap between clydes). However, for both, no link for PFOS could be established. In the case of Menogorrhea, PFOAs and PFOSs were reduced by 0.2% and 0/3% respectively (Menogorrhea: heavy bleeding). For light bleeding (Hypomenorrhea) however, no link could be established between exposure and menstrual cycle as well. The studies that don’t support this hypothesis fully are Lynge (2014) and Kritsen et al (2013). In Lynge's (2014), cross-sectional study, 1623 pregnant women were taken from ages 19-49 and were exposed to a median of 1.5% of PFOA and 8.0% PFOS. The results revealed that with PFOA exposure, longer cycles were 1.8% higher, but there was no association between PFOS (longer cycle length is > 31 days.) With shorter and irregular cycles, however, no link between PFOA and PFOS could be established. In Kristen et al (2013), 267 female offspring that were young (1988) were followed up 20 years later (2008) and despite median exposure of 3.6% of PFOAs and 21.1% of PFOS, no association was drawn between the cycle length and the number of follicles in the ovary with the exposure. These results reveal how all data still available is still ambiguous and to get a stronger correlation, more studies need to be conducted.

Disorders

Ovarian Insufficiency

Ovarian Aging is a natural process that can be classified as the last step of menopause when the quality of oocytes reduces and there is a depletion in the follicles. This causes a loss in ovarian function which in turn results in cycles irregularly and infertility. The characteristics of ovarian ageing haven't been fully categorized yet, however, one of the

factors that may cause it to come early is exposure to PFAS. When it happens before the age of 40 with elevated FSH levels, it is considered a disorder called Primary Ovarian Insufficiency (POI), which is what we'll be exploring today. In Zhang et al (2018)'s case-control study of 240 women, it was found that when women were exposed to 8.4% of PFOA and 8.2% of PFOS, they had elevated risks of POI (with +3.8% of PFOA and +2.8% with PFOS.) Ovarian insufficiency not only leads to infertility but also a higher risk of mortality due to ovarian disorders (Jacobsen et al. 2003) disease and possible death due to problems in the cardiovascular (Hu et al. 1999; van der Schouw et al. 1996) It also leads to osteoporosis (Kritz-Silverstein and Barrett-Connor, 1993) and other chronic conditions (Shuster et al., 2010). In Taylor et al. (2014)'s study, out of 2732 women taken from NHANES (National Health and Nutrition Examination Survey) between 1998- 2010, natural menopause and hysterectomy were increased by 2.4% and 2.8% from PFOAs exposure (>40%) respectively. However, no association could be found with PFOS exposure. Moreover, in Knox et al. (2011), a cross-sectional study of 25957 participants (mean age: 42-65 years) that were going to experience menopause were taken and exposed to 23.6% of PFOAs, and results revealed that they experience menopause earlier. In a cohort study of women recruited during 2005–2006, Dhingra et al. (2016) had no significant association between PFOA exposure and natural menopause incidence.

PCOS (Polycystic Ovary Syndrome)

Polycystic Ovary Syndrome is another endocrine disorder that is affected if a woman is exposed to PFA. According to Normal et al. (2007) in PCOS, many of its adverse effects include menstrual dysfunction, infertility, obesity, acne, hirsutism, possible Type 2 diabetes, cardiovascular disease, and many more. In a study conducted by Wang, Zhou et al. 2019, 180 infertile PCOS women and 18- healthy controls were considered. They were from ages 20-40 and exposed to 5.1% of PFOAs and 4.1% of the process. This revealed a positive dose-response relationship between PFDoA serum concentrations and risks of PCOS-related infertility; however, no significant associations were observed for PFBS and other EDCs.

Ovarian Cancer

Ovarian cancer is considered the growth of cells that forms inside the ovaries. They destroy healthy body tissue. While PFA exposure and ovarian cancer studies are limited, the ones that have been conducted have not found strong correlations between the two. The two studies by Barry et al., 2013 and Vieira et al., 2013 have not found a strong correlation but the number of cases in each study was small. Thus, while the studies are a step toward the better, they are not enough to assess the risk of ovarian carcinogenicity due to PFAS exposure.

Discussion

Summary of findings

The findings from the studies conducted have revealed that PFAS exposure target the ovary, specifically with the process of folliculogenesis. This is observed in the studies of Bellingham et al. (2009), Feng et al. (2015), Domínguez et al. (2016), Chen et al. (2017), Du et al. (2019), Hallberg et al. (2019), and López-Arellano et al. (2019) They reveal how PFAS exposure alters the development of the follicle and the oocyte and thus diminish the ovarian reserve by various mechanisms that include PPAR activation, disruption of gap junction intercellular communication, oxidative stress and thyroid hormone disruption. In mostly all of the studies, the associations between PFAS exposure and ovarian function, despite large sample sizes, varying age groups, and geographical locations, were not consistent.

However some notable studies like Kristen et al. (2013) found that PFOA and PFOS exposure was associated with delayed menarche, Fei et al. (2009) associated the exposure to irregular menstrual circles, Zhang et al. (2018) associated this exposure with increased risk of primary ovarian insufficiency and Knox et al. (2011) and Taylor et al. (2014) associated it with early menopause.

While there is a correlation amongst the factors, there are various problems such as reverse causation and self-reporting biases. In late menarche and PFAS exposure (Wu et al. 2015), the relation established could be due to reverse causation rather than the toxic effect of PFAS, which means that the physiological changes during reproductive growth and

maturation in girls may have a considerable influence on serum PFAS concentrations. Studies that assessed links between PFAS and early menopause could also be a product of reverse causation related to the presence or volume of menstrual bleeding. Since most of the studies, also had to report many of the symptoms themselves (when it came to the timing of menarche, menstrual cycle length, and age at menopause) self-reporting bias may have occurred which may have tampered with the results. Given the inconsistency in previous findings and lack of longitudinal evidence, no causal inferences can be drawn at this time based on this body of literature.

Future directions

While this review did not result in an established relationship between the two factors: ovarian function and PFAS exposure, it did bring forward the lack of evidence surrounding them. This is a high risk as with increasing days, come increasing exposure and various studies show how they might contribute to ovarian function. Humans that have been exposed to PFAS may have adverse health effects n their reproductive and overall health which include: disruption of fertility, reproductive lifespan, and regulation of skeletal, cardiovascular, and brain functions. In the following ways, the scientific community can help establish a correlation between the two factors.

More prospective cohort designs

With almost all of the studies observed, the main problem that occurs is the possibility of reverse causation. With a prospective cohort study, a causal relationship between PFAS exposure and ovarian function can be established as these studies include long-term follow-up of participants, repeated measurements, and prospective assessment of ovarian function.

Exploring the alternatives

Since various alternatives to PFOA and PFOS have emerged (Ateia et al. 2019), it is important to measure their adverse effects on ovarian function and reproductive disorders as well. A notable new alternative is the 'GenX chemicals that are used to make high-performance fluoropolymers and non-stick coatings without the use of PFOA.

Effects of a mixture of EDCs

PCB and PBDEs have been explored before when considering ovarian function. However, only when a mixture of endocrine disruptors will be taken into account, will people get the actual big picture behind their disorders. Environmental endocrine disruption is most often not due to the effect of a single compound, but rather due to co-exposure to mixtures of chemicals at low concentrations. Thus, future research should examine the effects of exposure to a mixture of persistent and non-persistent EDCs on ovarian health.

Conclusion

It is important for research and public health to have a strong correlation between PFAS exposure and abnormal ovarian function to eliminate the problems and take regulatory actions by it. Millions of people are exposed to PFAS worldwide, via water and by other sources mentioned, and so analyzing the link between them and the ovary (which is a primary regulator of reproductive and endocrine function in a female) is important as the adverse effects could be extremely serious. In conclusion, at present, there is insufficient evidence to determine a causal relationship between PFAS exposure and ovarian function due to methodological problems, so experimental studies with the above-mentioned future directions should be future research priorities.

References

1. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for perfluoroalkyalperfluoroalkyl. 2018. https://www.atsdr.cdc.gov/sites/peer_review/tox_profile_perfluoroalkyls.html

2. Ateia M, Maroli A, Tharayil N, Karanfil T. The overlooked short and short and ultrashort-chain poly- and perfluorinated substances: a review.
3. Atsma F, Bartelink M-LEL, Grobbee DE, van der Schouw YT. Postmenopausal status and early menopause as independent factors for cardiovascular disease: a meta-analysis. Menopause 2006;13:265–279.
4. Banks RE, Tatlow JC. Organofluorine chemistry: nomenclature and historical landmarks. In: Organofluorine Chemistry. Boston: Springer US, 1994,1–24
5. Barber JL, Berger U, Chaemfa C, Huber S, Jahnke A, Temme C, Jones KC. Analysis of per- and polyfluorinated alkyl substances in air samples from Northwest Europe. J Environ Monit 2007;9:530–541.
6. Barry V, Winquist A, Steenland K. Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. Environ Health Perspect 2013;121:1313–1318.
7. Bartell SM, Calafat AM, Lyu C, Kato K, Ryan PB, Steenland K. Rate of decline in serum PFOA concentrations after granular activated carbon filtration at two public water systems in Ohio and West Virginia. Environ Health Perspect 2010;118:222–228.
8. Begley TH, White K, Honigfort P, Twaroski ML, Neches R, Walker RA. Perfluorochemicals: potential sources of and migration from food packaging. Food Addit Contam 2005;22:1023–1031.
9. Biegel LB, Liu RCM, Hurtt ME, Cook JC. Effects of ammonium perfluorooctanoate on Leydig-cell function: in vitro, in vivo, and ex vivo studies. Toxicol Appl Pharmacol 1995;134:18–25.
10. Bjermo H, Darnerud PO, Pearson M, Barbieri HE, Lindroos AK, Nälsén C, Lindh CH, Jönsson BAG, Glynn A. Serum concentrations of perfluorinated alkyl acids and their associations with diet and personal characteristics among Swedish adults. Mol Nutr Food Res 2013;57:2206–2215.
11. Bjork JA, Wallace KB. Structure-activity relationships and human relevance for perfluoroalkyl acid-induced transcriptional activation of peroxisome proliferation in liver cell cultures. Toxicol Sci 2009;111:89–99.
12. Boone JS, Vigo C, Boone T, Byrne C, Ferrario J, Benson R, Donohue J, Simmons JE, Kolpin DW, Furlong ET et al. Per- and polyfluoroalkyl substances in source and treated drinking waters of the United States. Sci Total Environ 2019;653:359–369.
13. Boronow KE, Brody JG, Schaider LA, Peaslee GF, Havas L, Cohn BA. Serum concentrations of PFASs and exposure-related behaviours in African American and non-Hispanic white women. J Expo Sci Environ Epidemiol 2019;29:206–217.
14. Bradley EL, Read WA, Castle L. Investigation into the migration potential of coating materials from cookware products. Food Addit Contam 2007;24:326–335.
15. Braun JM, Gennings C, Hauser R, Webster TF. What can epidemiological studies tell us about the impact of chemical mixtures on human health? Environ Health Perspect 2016;124:A6–A9.
16. Brede E, Wilhelm M, Göen T, Müller J, Rauchfuss K, Kraft M, Hölzer J. Two-year follow-up biomonitoring pilot study of residents' and controls' PFC plasma levels after PFOA reduction in public water system in Arnsberg, Germany. Int J Hyg Environ Health 2010;213:217–223.
17. Buck RC, Franklin J, Berger U, Conder JM, Cousins IT, de Voogt P, Jensen AA, Kannan K, Mabury SA, van Leeuwen SPJ. Perfluoroalkyl and polyfluoroalkyl substances in the environment: terminology, classification, and origins. Integr Environ Assess Manag 2011;7:513–541.
18. Burger HG, Hale GE, Robertson DM, Dennerstein L. A review of hormonal changes during the menopausal transition: focus on findings from the Melbourne Women's Midlife Health Project. Hum Reprod Update 2007;13:559–565.

19. Butenhoff JL, Olsen GW, Pfahles-Hutchens A. The applicability of biomonitoring data for perfluorooctanesulfonate to the environmental public health continuum. Environ Health Perspect 2006;114:1776–1782.
20. Calafat AM, Wong LY, Kuklenyik Z, Reidy JA, Needham LL. Polyfluoroalkyl chemicals in the U.S. population: data from the national health and nutrition examination survey (NHANES) 2003-2004 and comparisons with NHANES 1999-2000. Environ Health Perspect 2007;115:1596–1602.
21. Caserta D, Mantovani A, Marci R, Fazi A, Ciardo F, La Rocca C, Marangoni F, Moscarini M. Environment and women's reproductive health. Hum Reprod Update 2011;17:418–433.
22. Centers for Disease Control. National Report on Human Exposure to Environmental Chemicals, 2019. https://www.cdc.gov/exposure report/index.html
23. Centers for Disease Control and Prevention. Fourth Report on Human Exposure to Environmental Chemicals. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2009. https://www.cdc.gov/exposurereport/
24. Chen W-L, Bai F-Y, Chang Y-C, Chen P-C, Chen C-Y. Concentrations of perfluoroalkyl substances in foods and the dietary exposure among Taiwan's general population and pregnant women. J Food Drug Anal 2018;26:994–1004.
25. Chen Y, Zhou L, Xu J, Zhang L, Li M, Xie X, Xie Y, Luo D, Zhang D, Yu X et al. Maternal exposure to perfluorooctanoic acid inhibits luteal function via oxidative stress and apoptosis in pregnant mice. Reprod Toxicol 2017;69:159–166.
26. Christensen KY, Maisonet M, Rubin C, Holmes A, Calafat AM, Kato K, Flanders WD, Heron J, McGeehin MA, Marcus M. Exposure to polyfluoroalkyl chemicals during pregnancy is not associated with offspring age at menarche in a contemporary British cohort. Environ Int 2011;37:129–135.
27. Clancy KBH. Reproductive ecology and the endometrium: physiology, variation, and new directions. Am J Phys Anthropol 2009;140: 137–154.
28. Clark KL, Ganesan S, Keating AF. Impact of toxicant exposures on ovarian gap junctions. Reprod Toxicol 2018;81:140–146.
29. Craig ZR, Ziv-Gal A. Pretty good or pretty bad? The ovary and chemicals in personal care products. Toxicol Sci 2018;162:349–360.
30. Dallaire R, Dewailly E, Pereg D, Dery S, Ayotte P. Thyroid function and plasma concentrations of polyhalogenated compounds in Inuit adults. Environ Health Perspect 2009;117:1380–1386.
31. Dhingra R, Darrow LA, Klein M, Winquist A, Steenland K. Perfluorooctanoic acid exposure and natural menopause: a longitudinal study in a community cohort. Environ Res 2016;146:323–330.
32. Dhingra R, Winquist A, Darrow LA, Klein M, Steenland K. A study of reverse causation: examining the associations of perfluorooctanoic acid serum levels with two outcomes. Environ Health Perspect 2017;125:416–421.
33. Diamanti-Kandarakis E, Bourguignon J-P, Giudice LC, Hauser R, Prins GS, Soto AM, Zoeller RT, Gore AC. Endocrine-disrupting chemicals: An Endocrine Society scientific statement. Endocr Rev 2009;30:293.
34. Dijkstra G, de Rooij DG, de Jong FH, van den Hurk R. Effect of hypothyroidism on ovarian follicular development, granulosa cell proliferation and peripheral hormone levels in the prepubertal rat. Eur J Endocrinol 1996;134:649–654.
35. Ding N, Harlow SD, Batterman S, Mukherjee B, Park SK. Longitudinal trends in perfluoroalkyl and polyfluoroalkyl substances among multiethnic midlife women from 1999 to 2011: the Study of Women's Health Across the Nation. Environ Int 2020;135:105381.

36. Domingo JL, Jogsten IE, Eriksson U, Martorell I, Perelló G, Nadal M, Bavel, van B. Human dietary exposure to perfluoroalkyl substances in Catalonia. Spain Temporal trend Food Chem 2012;135:1575–1582.
37. Domingo JL, Nadal M. Per- and polyfluoroalkyl substances (PFASs) in food and human dietary intake: a review of the recent scientific literature. J Agric Food Chem 2017;65:533–543.
38. Domingo JL, Nadal M. Human exposure to per- and polyfluoroalkyl substances (PFAS) through drinking water: a review of the recent scientific literature. Environ Res 2019;177:108648.
39. Environmental Working Group. Report: up to 110 million Americans could have PFAS-contaminated drinking water. 2018.
40. Eriksson U, Kärrman A, Rotander A, Mikkelsen B, Dam M. Perfluoroalkyl substances (PFASs) in food and water from Faroe Islands. Environ Sci Pollut Res 2013;20:7940–7948.
41. Eriksson U, Mueller JF, Toms L-ML, Hobson P, Kärrman A. Temporal trends of PFSAs, PFCAs and selected precursors in Australian serum from 2002 to 2013. Environ Pollut 2017;220:168–177.
42. Fei C, McLaughlin JK, Lipworth L, Olsen J. Maternal levels of perfluorinated chemicals and subfecundity. Hum Reprod 2009;24:1200–1205.
43. Felizeter S, McLachlan MS, De Voogt P. Root uptake and translocation of perfluorinated alkyl acids by three hydroponically grown crops. J Agric Food Chem 2014;62:3334–3342.
44. Feng X, Cao X, Zhao S, Wang X, Hua X, Chen L, Chen L. Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring. Toxicol Sci 2017;155:409–419.
45. Feng X, Wang X, Cao X, Xia Y, Zhou R, Chen L. 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 2015;148:368–379.
46. Fromme H, Dreyer A, Dietrich S, Fembacher L, Lahrz T, Völkel W. Neutral polyfluorinated compounds in indoor air in Germany – the LUPE 4 study. Chemosphere 2015;139:572–578.
47. Gebbink WA, Glynn A, Darnerud PO, Berger U. Perfluoroalkyl acids and their precursors in Swedish food: the relative importance of direct and indirect dietary exposure. Environ Pollut 2015;198:108–115.
48. Glynn A, Berger U, Bignert A, Ullah S, Aune M, Lignell S, Darnerud PO. Perfluorinated alkyl acids in blood serum from primiparous women in Sweden: serial sampling during pregnancy and nursing, and temporal trends 1996–2010. Environ Sci Technol 2012;46:9071–9079.
49. Goosey E, Harrad S. Perfluoroalkyl substances in UK indoor and outdoor air: spatial and seasonal variation, and implications for human exposure. Environ Int 2012;45:86–90.
50. Gorrochategui E, Pérez-Albaladejo E, Casas J, Lacorte S, Porte C. Perfluorinated chemicals: differential toxicity, inhibition of activity and alteration of cellular lipids in human placental cells. Toxicol Appl Pharmacol 2014;277:124–130.
51. Grindler NM, Allsworth JE, Macones GA, Kannan K, Roehl KA, Cooper AR. Persistent organic pollutants and early menopause in U.S. women. Rosenfeld CS (ed). PLoS One 2015;10:e0116057.
52. Hallberg I, Kjellgren J, Persson S, Örn S, Sjunnesson Y. Perfluorononanoic acid (PFNA) alters lipid accumulation in bovine blastocysts after oocyte exposure during in vitro maturation. Reprod Toxicol 2019;84:1–8.
53. Han X, Mingoia R, Snajdr S, Yang C, Nabb D. Uptake of perfluorooctanoate in freshly isolated hepatocytes from male and female rats. Toxicol Lett 2008;181:81–86.
54. Han X, Snow TA, Kemper RA, Jepson GW. Binding of perfluorooctanoic acid to rat and human plasma proteins. Chem Res Toxicol 2003;16:775–781.

55. Harada K, Inoue K, Morikawa A, Yoshinaga T, Saito N, Koizumi A. Renal clearance of perfluorooctane sulfonate and perfluorooctanoate in humans and their species-specific excretion. Environ Res 2005;99:253–261.
56. Harley KG, Berger KP, Kogut K, Parra K, Lustig RH, Greenspan LC, Calafat AM, Ye X, Eskenazi B. Association of phthalates, parabens and phenols found in personal care products with pubertal timing in girls and boys. Hum Reprod 2019;34:109–117.
57. Haug LS, Huber S, Becher G, Thomsen C. Characterisation of human exposure pathways to perfluorinated compounds - comparing exposure estimates with biomarkers of exposure. Environ Int 2011a;37:687–693.
58. Haug LS, Huber S, Schlabach M, Becher G, Thomsen C. Investigation on per- and polyfluorinated compounds in paired samples of house dust and indoor air from Norwegian homes. Environ Sci Technol 2011b;45:7991–7998.
59. Haug LS, Salihovic S, Jogsten IE, Thomsen C, van Bavel B, Lindström G, Becher G. Levels in food and beverages and daily intake of perfluorinated compounds in Norway. Chemosphere 2010;80: 1137–1143.
60. Heffernan AL, Cunningham TK, Drage DS, Aylward LL, Thompson K, Vijayasarathy S, Mueller JF, Atkin SL, Sathyapalan T. 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 2018;221:1068–1075.
61. Hess KA, Chen L, Larsen WJ. The ovarian blood follicle barrier is both charge- and size-selective in mice. Biol Reprod 1998;58:705–711.
62. Hill PJ, Taylor M, Goswami P, Blackburn RS. Substitution of PFAS chemistry in outdoor apparel and the impact on repellency performance. Chemosphere 2017;181:500–507.
63. Hillier SG, Whitelaw PF, Smyth CD. Follicular oestrogen synthesis: the “two-cell, two-gonadotrophin” model revisited. Mol Cell Endocrinol 1994;100:51–54.
64. Hu FB, Grodstein F, Hennekens CH, Colditz GA, Johnson M, Manson JE, Rosner B, Stampfer MJ. Age at natural menopause and risk of cardiovascular disease. Arch Intern Med 1999;159:1061–1066.
65. Hu XC, Andrews DQ, Lindstrom AB, Bruton TA, Schaider LA, Grandjean P, Lohmann R, Carignan CC, Blum A, Balan SA et al. Detection of poly- and perfluoroalkyl substances (PFASs) in U.S. drinking water linked to industrial sites, military fire training areas, and wastewater treatment plants. Environ Sci Technol Lett 2016;3:344–350.
66. Interstate Technology Regulatory Council. PFAS Fact Sheets. 2020. https://pfas-1.itrcweb.org/.
67. Jacobsen BK, Heuch I, Kvåle G. Age at natural menopause and all-cause mortality: a 37-year follow-up of 19,731 Norwegian women. Am J Epidemiol 2003;157:923–929.
68. Jensen AA, Leffers H. Emerging endocrine disrupters: perfluoroalkylated substances. Int J Androl 2008;31:161–169.
69. Jian J-M, Guo Y, Zeng L, Liang-Ying L, Lu X, Wang F, Zeng EY. Global distribution of perfluorochemicals (PFCs) in potential human exposure source–a review. Environ Int 2017;108:51–62.
70. Jin YH, Liu W, Sato I, Nakayama SF, Sasaki K, Saito N, Tsuda S. PFOS and PFOA in environmental and tap water in China. Chemosphere 2009;77:605–611.
71. Jones PD, Hu W, De Coen W, Newsted JL, Giesy JP. Binding of perfluorinated fatty acids to serum proteins. Environ Toxicol Chem 2003;22:2639–2649.
72. Kantiani L, Llorca M, Sanchís J, Farré M, Barceló D. Emerging food contaminants: a review. Anal Bioanal Chem 2010;398:2413–2427.
73. Karásková P, Venier M, Melymuk L, Becanová J, Vojta ˇ ˇ S, Prokes R, ˇ Diamond ML, Klánová J. Perfluorinated alkyl substances (PFASs) in household dust in Central Europe and North America. Environ Int 2016;94:315–324.

74. Kissa E. Fluorinated Surfactants and Repellents. Marcel Dekker, 2011
75. Knox JT, Javins B, Frisbee SJ, Shankar A, Ducatman AM. Implications of early menopause in women exposed to perfluorocarbons. J Clin Endocrinol Metab 2011;96:1747–1753.
76. Komar CM. Peroxisome proliferator-activated receptors (PPARs) and ovarian function – implications for regulating steroidogenesis, differentiation, and tissue remodeling. Reprod Biol Endocrinol 2005;3:41.
77. Komar CM, Braissant O, Wahli W, Curry TE. Expression and localization of PPARs in the rat ovary during follicular development and the periovulatory period. Endocrinology 2001;142:4831–4838.
78. Kritz-Silverstein D, Barrett-Connor E. Early menopause, number of reproductive years, and bone mineral density in postmenopausal women. Am J Public Health 1993;83:983–988.
79. Kubwabo C, Stewart B, Zhu J, Marro L. Occurrence of perfluorosulfonates and other perfluorochemicals in dust from selected homes in the city of Ottawa, Canada. J Environ Monit 2005;7: 1074–1078.
80. Kudo N, Katakura M, Sato Y, Kawashima Y. Sex hormone-regulated renal transport of perfluorooctanoic acid. Chem Biol Interact 2002;139:301–316.
81. Langer V, Dreyer A, Ebinghaus R. Polyfluorinated compounds in residential and nonresidential indoor air. Environ Sci Technol 2010;44:8075–8081.
82. Lau C, Thibodeaux JR, Hanson RG, Rogers JM, Grey BE, Stanton ME, Butenhoff JL, Stevenson LA. Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. II: Postnatal Evaluation Toxicol Sci 2003;74:382–392.
83. Lee JH, Lee CK, Suh C-H, Kang H-S, Hong C-P, Choi S-N. Serum concentrations of per- and poly-fluoroalkyl substances and factors associated with exposure in the general adult population in South Korea. Int J Hyg Environ Health 2017;220:1046–1054.
84. Lewis RC, Johns LE, Meeker JD. Serum biomarkers of exposure to perfluoroalkyl substances in relation to serum testosterone and measures of thyroid function among adults and adolescents from NHANES 2011-2012. Int J Environ Res Public Health 2015;12:6098–6114.
85. Li Y, Fletcher T, Mucs D, Scott K, Lindh CH, Tallving P, Jakobsson K. Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. Occup Environ Med 2018;75:46–51.
86. Liu C, Du Y, Zhou B. Evaluation of estrogenic activities and mechanism of action of perfluorinated chemicals determined by vitellogenin induction in primary cultured tilapia hepatocytes. Aquat Toxicol 2007;85:267–277.
87. López-Arellano P, López-Arellano K, Luna J, Flores D, Jiménez-Salazar J, Gavia G, Teteltitla M, Rodríguez JJ, Domínguez A, Casas E et al. Perfluorooctanoic acid disrupts gap junction intercellular communication and induces reactive oxygen species formation and apoptosis in mouse ovaries. Environ Toxicol 2019;34:92–98.
88. Lopez-Espinosa M-J, Fletcher T, Armstrong B, Genser B, Dhatariya K, Mondal D, Ducatman A, Leonardi G. Association of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) with age of puberty among children living near a chemical plant. Environ Sci Technol 2011;45:8160–8166.
89. Lopez-Espinosa M-J, Mondal D, Armstrong BG, Eskenazi B, Fletcher T. Perfluoroalkyl substances, sex hormones, and insulin-like growth factor-1 at 6-9 years of age: a cross-sectional analysis within the C8 health project. Environ Health Perspect 2016;124:1269–1275.
90. Lorber M, Eaglesham GE, Hobson P, Toms L-ML, Mueller JF, Thompson JS. The effect of ongoing blood loss on human serum concentrations of perfluorinated acids. Chemosphere 2015;118: 170–177.
91. Lorber M, Egeghy PP. Simple intake and pharmacokinetic modelling to characterize exposure of Americans to perfluorooctanoic acid, PFOA. Environ Sci Technol 2011;45:8006–8014.

92. Lum KJ, Sundaram R, Barr DB, Louis TA, Buck Louis GM. Perfluoroalkyl chemicals, menstrual cycle length, and fecundity. Epidemiology 2017;28:90–98. Downloaded from https://academic.oup.com/humupd/advance-article-abstract/doi/10.1093/humupd/dmaa018/5848465
93. Mak YL, Taniyasu S, Yeung LWY, Lu G, Jin L, Yang Y, Lam PKS, Kannan K, Yamashita N. Perfluorinated compounds in tap water from China and several other countries. Environ Sci Technol 2009;43: 4824–4829.
94. Maras M, Vanparys C, Muylle F, Robbens J, Berger U, Barber JL, Blust R, De Coen W. Estrogen-like properties of fluorotelomer alcohols as revealed by MCF-7 breast cancer cell proliferation. Environ Health Perspect 2006;114:100–105.
95. Mashayekhi V, Tehrani KHME, Hashemzaei M, Tabrizian K, Shahraki J, Hosseini M-J. Mechanistic approach for the toxic effects of perfluorooctanoic acid on isolated rat liver and brain mitochondria. Hum Exp Toxicol 2015;34:985–996.
96. McCoy JA, Bangma JT, Reiner JL, Bowden JA, Schnorr J, Slowey M, O'Leary T, Guillette LJ, Parrott BB. Associations between perfluorinated alkyl acids in the blood and ovarian follicular fluid and ovarian function in women undergoing assisted reproductive treatment. Sci Total Environ 2017;605–606:9–17. McEwen BS, Alves SE. Estrogen actions in the central nervous system. Endocr Rev 1999;20:279–307.
97. Mondul AM, Rodriguez C, Jacobs EJ, Calle EE. Age at natural menopause and cause-specific mortality. Am J Epidemiol 2005;162: 1089–1097.
98. Monroy R, Morrison K, Teo K, Atkinson S, Kubwabo C, Stewart B, Foster WG. Serum levels of perfluoroalkyl compounds in human maternal and umbilical cord blood samples. Environ Res 2008;108: 56–62.
99. Must A, Phillips SM, Naumova EN, Blum M, Harris S, Dawson-Hughes B, Rand WM. Recall of early menstrual history and menarcheal body size: after 30 years, how well do women remember? Am J Epidemiol 2002;155:672–679.
100. Noorlander CW, van Leeuwen SPJ, te Biesebeek JD, Mengelers MJB, Zeilmaker MJ. Levels of perfluorinated compounds in food and dietary intake of PFOS and PFOA in the Netherlands. J Agric Food Chem 2011;59:7496–7505.