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Research Article

PFAS Toxicity and Female Reproductive Health: A Review of the Evidence and Current State of Knowledge

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Abstract. Per- and polyfluoroalkyl substances (PFAS) constitute a class of synthetic chemicals extensively utilized in various consumer products and industrial applications. Characterized by their remarkable persistence, PFAS chemicals resist degradation, perpetuating their presence in the environment for an indefinite period. Human exposure to PFAS occurs through multiple pathways, including contaminated food, water, air, and products, resulting in widespread detection in biological matrices such as blood and urine. Exposure to PFAS has also been linked to adverse reproductive outcomes, yet the impact on female reproductive health remains poorly understood. This review synthesizes recent findings on the PFAS-female reproductive health connection, highlighting the effects on ovarian function, hormone regulation, and pregnancy outcomes. The evidence suggests that PFAS exposure is associated with reduced fertility, increased risk of miscarriage, and altered menstrual cycle dynamics. The review also explores the underlying mechanisms, including endocrine disruption and oxidative stress. The implications of these findings on female reproductive health are discussed, emphasizing the need for further research and policy changes to mitigate PFAS exposure and protect female reproductive physiology.

Keywords: PFAS; Female fertility; Pregnancy; Endocrine disruption; Menstrual cycle

INTRODUCTION

Per- and polyfluoroalkyl substances (PFAS), also known as forever chemicals are a large family of synthetic organofluorine chemicals with diverse applications across various industries. First discovered in the 1930s, they entered commercial production on a large scale in the 1940s (OECD, 2021; ITRC, 2020). Comprising over 4,730 identified chemicals (Zhang et al., 2022), PFAS are characterized by the presence of at least one fluorine atom bonded to carbon atoms, forming a robust carbon-fluorine bond. This unique property renders PFAS versatile for various applications, including electronics, aerospace, construction, and consumer products (Gaines, 2022). However, it also confers exceptional resistance to degradation in the environment, requiring temperatures above 1,100 °C for destruction (OECD, 2021). PFAS can exist in various ionic states, including cations, anions, and zwitterions, which determine their electrical charge, physical, and chemical properties. These properties control their fate and transport in the environment. The carbon-fluorine groups in PFAS can be linked to various chemical groups, making them useful for a wide range of applications. However, the widespread use of PFAS has led to various environmental release pathways, including wear and tear of consumer products, fugitive emissions, manufacturing waste streams, disposal of PFAS-containing materials, and spills. This has resulted in the aggregation of PFAS in wastewater treatment plant effluent and sludges, posing a threat to wildlife and human health. Exposure to PFAS can occur through direct involvement in the manufacturing process, professional use of materials containing PFAS, use of consumer products containing PFAS, and exposure to environmental releases (Brunn et al., 2023; De Silva et al., 2021). The persistence and mobility of PFAS in the environment, bioaccumulation in humans and wildlife, and potential toxicity raise significant concerns, highlighting the need for policy changes and mitigation strategies to protect human and environmental health.

The persistence of PFAS is a notable property, characterized by their resistance to degradation under natural conditions, posing a significant threat to the environment as long-lasting pollutants (Cousins et al., 2020). The half-life of a chemical, defined as the time required for its concentration to decrease by half in a specific medium, is a criterion for persistence. According to EU chemical regulation, chemicals with a half-life exceeding 60 days in water and 180 days in sediments or soil are considered very persistent (Cousins et al., 2020). Although the half-life of most PFAS is unknown, estimates suggest that some PFAS polymers can persist for over 1,000 years in soil, while non-polymeric PFAS can persist for over 40 years in water (Xu et al., 2020). Even when PFAS degrade, their degradation products often include other persistent PFAS (Bridger, 2023), earning them the name forever chemicals. PFAS are also bioaccumulative, building up in the human body and wildlife by binding to proteins in blood, such as albumin and fatty acid binding protein, rather than accumulating in fatty tissues like most bioaccumulative chemicals (Forsthuber et al., 2020; Lai et al., 2020; Khazaee, 2021). This bioaccumulation occurs through absorption, without excretion, leading to increased concentrations higher up the food chain.

The processing of PFAS varies across organisms, with differences observed between sexes, species, and structures. In humans, long-chain PFAS are eliminated slowly, taking years (e.g., PFHxS has a half-life in blood of up to 8.5 years), and tend to accumulate in protein-rich compartments like blood, liver, kidney, and bones (Cousins, 2022). In contrast, short-chain PFAS are eliminated more quickly (e.g., PFBS has a half-life in blood of 26 days), accumulating in different organs and tissues like lungs, kidneys, and the brain. While the behavior of PFAS in wildlife is not well understood, reports indicate bioaccumulation in water birds, wild boars, polar bears, and dolphins (Sudarshan et al., 2022; Fenton, 2021). Due to their high water solubility, PFAS are highly mobile in the environment, rapidly migrating through soil and leaching into groundwater (McMahon et al., 2022). Additionally, they can easily pass through conventional drinking water treatment facilities, contaminating drinking water. Furthermore, short-chain PFAS have been shown to migrate from soil to plants, accumulating in edible parts of fruits and vegetables (Xu et al., 2022). This highlights the potential for PFAS to enter the food chain and have far-reaching environmental and health impacts.

Exposure to PFAS has been linked to various adverse health effects, including immune system dysfunction, thyroid impairment, neurodevelopmental issues, cardiovascular disease, and reproductive problems (Mueller et al., 2020; Zheng et al., 2024). The human endocrine system, which regulates fertility hormones such as estrogen, Izumo1, Juno, and sperm receptors, is crucial for conception and ovulation. However, interference by PFAS and other endocrine-disrupting chemicals (EDCs) could lead to reproductive health challenges like hormone imbalance and infertility (Kim et al., 2019). While various natural and environmental factors influence reproductive success, evidence suggests that environmental chemicals like EDCs decrease reproductive success in many species, including vertebrates and invertebrates (Kim et al., 2020; Xie et al., 2021; Rickard et al., 2022). EDCs disrupt reproductive development by altering the function of endocrine system components. The risks posed by EDCs to wildlife and humans are a widespread concern, and global efforts are underway to develop advanced assessment methodologies (Barton-Maclaren et al., 2022).

METHODS

Literature Search

A comprehensive literature search was conducted using major databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search strategy employed a combination of keywords and Medical Subject Headings (MeSH) terms related to per- and polyfluoroalkyl substances (PFAS), reproductive health, endocrine disruption, and female reproductive disorders. The search terms used included "PFAS," "reproductive health," "menstrual cycle irregularities," "polycystic ovary syndrome (PCOS)," "endometriosis," "pregnancy outcomes," and "female reproductive tract disorders." The search was limited to English-language articles published between 2007 and 2024.

Paper Selection

Studies were selected based on their relevance to the research question, study design, and publication date. Two independent reviewers screened the titles and abstracts of retrieved articles, and potentially relevant studies were selected for full-text review.

Inclusion and Exclusion Criteria

Studies were included if they:

1. Investigated the association between PFAS exposure and female reproductive health outcomes.
2. Examined the effects of PFAS on hormone regulation and endocrine function.
3. Were published in English.
4. Were peer-reviewed articles.
5. Were published between the year 2000 and 2024.

Studies were excluded if they:

1. Were conference proceedings, or editorials.
2. Did not focus on human subjects.
3. Did not examine PFAS exposure.
4. Were not relevant to female reproductive health.
5. Were published before the year 2000.

Study Selection

A total of 461 studies were identified through the literature search. After removing duplicates and applying the inclusion and exclusion criteria, 227 studies remained. Two independent reviewers screened the titles and abstracts, and 148 studies were selected for full-text review. Following full-text review, 106 studies met the final inclusion criteria.

SIZE-TOXICITY RELATIONSHIP OF PFAS MOLECULES

Per- and polyfluoroalkyl substances (PFAS) are distinct from other fluorinated compounds, such as Freon (chlorofluorocarbons) and Teflon (polytetrafluoroethylene, PTFE), due to their unique chemical structure. PFAS are characterized by a hydrophobic fluorinated chain linked to diverse functional groups, exhibiting variability in chain length and chemical functionality. In contrast, Freon features chlorine and fluorine bonded to carbon, while Teflon comprises polymerized tetrafluoroethylene monomers (-CF2-CF2-), with both possessing fixed molecular structures. The sizes and structures of PFAS molecules vary widely, ranging from short-chain compounds with seven or less carbon atoms to long-chain compounds with eight or more carbon atoms (Peritore et al., 2023). This variability in molecular size and structure contributes to their differing properties and potential environmental and health impacts.

Short-chain PFAS (Figure 1), such as PFBS (perfluorobutane sulfonate) and PFHxS (perfluorohexane sulfonate), have smaller molecular sizes and are more water-soluble than their long-chain counterparts (Grgas et al., 2023). While considered less toxic, short-chain PFAS have still been linked to environmental contamination and human health concerns. However, it is the long-chain PFAS that have created the most significant problems due to their persistence, bioaccumulation, and toxicity. Long-chain PFAS, such as PFOA (perfluorooctanoic acid) and PFOS (perfluorooctane sulfonate), have larger molecular sizes and are more persistent in the environment (Grgas et al., 2023). These compounds have been widely used in industrial applications and have raised concerns due to their potential health impacts, including cancer, reproductive issues, and immunological problems.

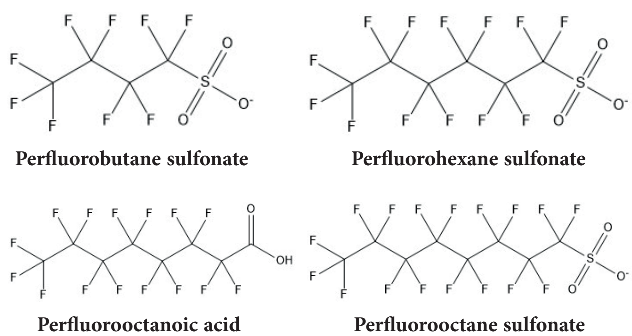

Figure 1: Some short-chain and long-chain PFAS

SOURCES AND PATHWAYS OF PFAS EMISSION

PFAS are ubiquitous in everyday products, having been used in a wide range of applications since the 1940s due to their unique carbon-fluorine bond properties (Glüge et al., 2021). This bond structure makes PFAS the most persistent chemicals known today (Kurwadkar et al., 2022). As a result, people and wildlife are exposed to hundreds of PFAS simultaneously through various environmental routes. The major routes of exposure to PFAS include:

- Oil and gas refineries, where PFAS are employed as viscosity reducers in crude oil processing (ITRC, 2020; Brunn et al., 2023; NRDC, 2021; Neuwald et al., 2020; USEPA, 2022).
- Household products, including food coverings, cables, coated woods, solar panels, textiles, leather, and glasses (Korzeniowski, 2022; Fiedler et al., 2020).
- Firefighting facilities and training areas where fluorine-containing firefighting materials are stored, used, or released, such as those utilizing firefighting foams to extinguish liquid fires (Mazumder et al., 2023).
- Waste management facilities and areas of bio-solids production and application, with significant impacts associated with industrial wastewater discharges (Saliu and Sauvé, 2024).
- Certain pesticides contain PFAS as co-formulants, specifically as wetting agents, which can lead to PFAS contamination in agricultural and environmental settings (PAN Europe, 2023).
- Personal care products, such as skin and hair care cosmetics that contain PFAS for water-repellent properties (Whitehead et al., 2021).
- PFAS used in surface treatment for paper and printed products for food packaging (Straková et al., 2021).

These various exposure routes highlight the widespread presence and persistence of PFAS in our environment.

PFAS have been detected in rivers unrelated to manufacturing sites, indicating emissions from widespread sources (Pan et al., 2018). These diffuse sources include consumer products like: cleaning products, food packaging, hydraulic fluids, textiles, cabling and wiring, metal finishing and plating. These products release PFAS through washing and wear and tear (Commission for Environmental Cooperation, 2017). Additional sources include coatings like anti-graffiti paints (Zhang et al., 2021). From 1970, DuPont utilized the telomerization process to produce eight-carbon chain perfluoro compounds, specifically perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), by combining two key reactants, an organoiodine compound, known as the telogen, which served as the initiator molecule, and tetrafluoroethylene (TFE), a highly reactive gas referred to as the taxogen. The telomerization reaction involved the sequential addition of TFE units to the telogen, resulting in a growing polymer chain that ultimately yielded the desired eight-carbon chain perfluoro compounds, possessing exceptional properties such as non-stick surfaces, water and oil repellency, thermal stability, and chemical resistance (Travis, 2024). Fluorotelomer alcohols, such as 6:2 FTOH and 8:2 FTOH, are volatile and have been detected in high concentrations in indoor air at stores selling sports, textiles, and carpets materials (Schlummer, 2013). This is a significant source of human exposure to PFAS (Huang et al., 2019). The stability of the C-F bond poses a problem for waste disposal and incineration at very high temperatures is the only way to ensure PFAS destruction (Berg et al., 2022).

ENDOCRINE DISRUPTING CHEMICALS (EDC)

The endocrine system is a complex network of tissues and glands that produce and secrete hormones, which play a crucial role in regulating various bodily functions, including growth and development, sexual function, metabolism, reproduction, mood, and sleep (Endocrine Society, 2023). This intricate system comprises specialized endocrine glands composed of tissues and cells that have a secondary endocrine function, secreting a diverse range of hormones. Hormones have specific target cells, characterized by the presence of receptors that bind to the hormone, either on the cell surface or intracellularly. The hormone-receptor interaction initiates a cascade of biochemical reactions within the target cell, ultimately modifying its function or activity. The reproductive hormones (Figure 2) produced primarily in the ovaries (females) and testes (males), play a crucial role in regulating reproductive cycles (Atiya et al., 2021).

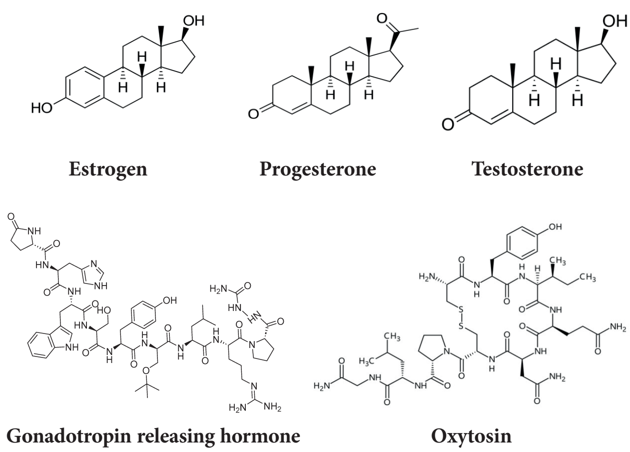

Figure 2: Human reproductive hormones

Hormones exert their effects on target cells through binding to specific receptors, which are cell proteins. The binding of a hormone to its corresponding receptor forms a hormone-receptor complex, triggering various responses within the target cells. Certain compounds can bind to hormone receptors, blocking them and leading to adverse effects in non-target organisms through an endocrine mode of action. These substances, known as endocrine disrupting chemicals (EDCs), are exogenous compounds that can disrupt the normal functioning of the endocrine system, potentially inducing adverse health effects (Ercan et al., 2022). EDCs mimic endogenous hormones, such as thyroid hormones, estrogens, and androgens by exhibiting similar activities or structures, influencing their metabolism and synthesis. These chemicals can impact various bodily systems by altering hormone regulation or normal function. Out of the estimated 85,000 synthetic chemicals in existence, a significant subset of over 1,000 compounds have been recognized as potential endocrine disruptors (Endocrine Society, 2023). The most well-studied EDCs include bisphenol A (BPA), phthalates, atrazine, polybrominated diphenyl ethers (PBDE), polychlorinated biphenyls (PCBs), perchlorate, and per- and polyfluoroalkyl substances (PFAS) (Nian et al., 2020; Lee et al., 2021). PFAS are recognized endocrine disrupting chemicals that have been linked to pervasive human health and environmental concerns. Research has demonstrated that PFAS could interfere with hormone regulation, exhibiting both agonist and antagonist properties that could disrupt endogenous hormone activity, thereby impairing reproductive, thyroid, and immune system function. Notably, their persistence, bioaccumulation, and widespread contamination of water, food, and consumer products necessitate rigorous scientific investigation and scrutiny, underscoring the importance of continued research into the implications of PFAS exposure.

PFAS AND THEIR ASSOCIATION WITH DISORDERS OF THE FEMALE REPRODUCTIVE SYSTEM

The female reproductive system is governed by a complex interplay of endocrine mechanisms, susceptible to interference by per- and polyfluoroalkyl substances (Figure 3). PFAS like PFOA, PFOS, and PFHxS have been associated with imbalances at the hormonal, metabolic, and reproductive systems levels, indicating their potential to disrupt normal hormone regulation and endocrine function (Fenton et al., 2021). Some of these PFAS are thought to disrupt crucial reproductive hormones, including progesterone, estradiol (E2), testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) (Lee et al., 2021). Moreover, there are suggestions that PFOS can alter important targets of the reproductive system, including thyroid hormone, human chorionic gonadotropin (hCG) levels, and prolactin, directly and indirectly by affecting reproductive tissues like breast and placental tissue (Pierozan and Karlsson, 2018; Bangma et al., 2020).

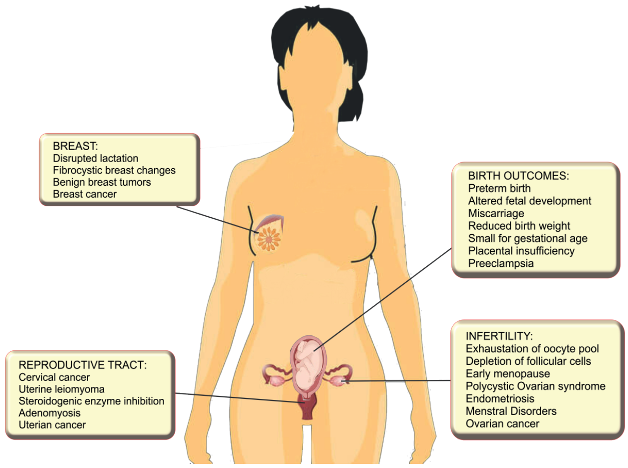

Figure 3: Disorders caused by PFAS to the female reproductive system

The ovary, a vital endocrine organ and female gonad, is a significant target for PFAS toxicity in females. It is responsible for folliculogenesis, oocyte maturation, and the production of female sex steroid and peptide hormones that regulate reproductive and non-reproductive functions (Athar et al., 2024). Environmental exposures to PFNA, PFOA, and PFOS have been linked to exhaustion of the oocyte pool, depletion of follicular cells, and earlier age at menopause, premature ovarian failure, and infertility (Ning et al., 2020). Furthermore, women exposed to PFNA, PFOS, PFDeA, and PFBS during IVF treatment have been found to have lower numbers of retrieved eggs, fertilized eggs, mature eggs, and high-quality embryos, suggesting that such exposure may negatively impact IVF success rates (Shen et al., 2024).

Research has established a link between PFAS exposure and fertility issues in pregnant women from Greenland, Poland, and Ukraine (Jørgensen et al., 2014). Higher levels of PFNA in the blood were associated with longer times to conceive and increased odds of infertility, both in the combined international group and in Greenlandic women specifically (Chen et al., 2021). Consistently, other studies have found that women with higher levels of PFOA and PFNA in their blood had a lower chance of getting pregnant compared to those with lower levels (Lum et al., 2017). While the evidence linking PFAS exposure to miscarriage is conflicting, a clear association has been found between increased umbilical cord concentrations of PFOS and preterm birth (Chen et al., 2021; Green et al., 2021). Furthermore, PFAS have been shown to promote endometriosis, a major cause of female infertility (Hammarstrand et al., 2021; Zhang et al., 2018). Women residing in heavily contaminated regions are particularly vulnerable to multiple reproductive dysfunctions (Rumph et al., 2022). Additionally, PFAS can affect human reproductive capacity by altering fetal development (Erinc et al., 2021). Elevated levels of PFOA in blood have been linked to an increased risk of miscarriage in early pregnancy (first trimester), a common complication in pregnancy (Wikstrom, 2021).

Short-chain PFAS, such as PFBS, PFHxS, PFTrDA, and GenX, have been found to impact hormone activities and physiology in non-occupationally exposed humans and other living organisms (Nian et al., 2020). Long-term exposure to PFOA, PFOS, and PFHxS leads to accumulation of these chemicals in women of child-bearing age, increasing exposure to the fetus and breastfed babies (Enyoh et al., 2023). The Minnesota Department of Health (MDH) recommends that women who are breastfeeding, pregnant, or planning to become pregnant take steps to reduce their exposure to PFAS. This is based on research showing that long-term exposure to PFAS could impact human health, particularly vulnerable populations like fetuses and infants. The Minnesota Pollution Control Agency (MPCA) and MDH have been investigating PFAS since 2002, and ongoing research continues to inform their guidance (https://www.pca.state.mn.us/sites/default/files/p-gen1-22g.pdf). Infant formula mixed with PFAS-contaminated water can result in higher exposure to PFAS, as babies consume more water per body weight than adults (Zhang et al., 2018). Research has shown an inverse association between perinatal exposure to certain PFAS (PFOS, PFOA, PFNA, PFHxS, or PFDA) and placental function, fetal growth, and infant birth weight (Kashino et al., 2020; Yao et al., 2021; Pearce et al., 2021). A study analyzing follicular fluid samples from Australian women detected 32 different types of PFAS in all samples. The study found correlations between specific PFAS levels and infertility issues, such as genital tract infections, polycystic ovary syndrome (PCOS), and endometriosis, although no significant link was found with fertilization success rates (Kim et al., 2020). Higher levels of PFNA, PFOA, and PFOS were linked to infertility issues, including PCOS, endometriosis, and genital tract infections, but were not significantly associated with fertilization rates (Kang et al., 2020; Campbell et al., 2016).

PFAS and Menstrual Cycle Irregularities

Research has consistently shown that exposure to PFAS can disrupt normal menstrual cycles, posing a potential threat to reproductive health and fertility (Lum et al., 2017). Animal studies have demonstrated that PFAS exposure can alter estrous cycles, leading to reduced frequency and disrupted reproductive function (Feng et al., 2015; Kato et al., 2015). Laboratory animals receive controlled, high-dose exposures, which may not accurately reflect real-world human exposure scenarios. Humans on the other hand, are exposed to lower doses over prolonged periods, often spanning decades. This chronic exposure leads to bioaccumulation, with PFAS detected in human blood, breast milk, and umbilical cord blood. In human populations, exposure to PFAS has been linked to irregular menstrual cycles (Lum et al., 2017), with a higher risk of cycles lasting seven days or more. Specifically, PFOS, PFNA, PFOA, and PFHxS have been associated with longer menstrual cycles, while higher levels of PFOA, PFOS, PFNA, and PFHxS have been linked to decreased reports of heavy or prolonged menstrual periods (menorrhagia) and increased reports of short or light menstrual periods (hypomenorrhea) (Zhou et al., 2017). The correlation between PFAS exposure and menstrual cycle irregularities has been further supported by studies examining menstrual cycle characteristics in women from the Norwegian Mother and Child Cohort (Singer et al., 2018) and in girls (Di Nisio et al., 2020). The exact mechanisms underlying these associations are not fully understood, but reduced menstrual bleeding and altered hormone regulation may contribute to the observed effects (Zhou et al., 2017). These findings suggest that PFAS exposure may have significant impacts on reproductive health and fertility.

The relationship between PFAS exposure and menstrual cycle length in couples attempting to conceive has been investigated. Findings showed that certain PFAS are associated with longer menstrual cycles, while others are associated with shorter cycles. Specifically, high serum PFOA levels were linked to longer menstrual cycles (25-31 days) compared to shorter cycles (≥32 days). Additionally, increased cycle length was observed with higher PFDA exposure, while decreased cycle length was seen with higher PFOA exposure (Lum et al., 2017). Similarly, another study found that women with higher PFOA exposure had longer menstrual cycles (≥32 days) and increased cycle irregularity (Lyngsø et al., 2014). Exposure to PFOA has also been linked to earlier age at menarche and a higher risk of irregular menstruation (Di Nisio et al., 2020). Overall, these findings suggest that PFAS exposure may impact menstrual cycle regulation and reproductive health.

PFAS and Female Reproductive Tract Disorders

Polycystic ovary syndrome (PCOS) is a prevalent hormonal disorder affecting women of reproductive age, significantly contributing to female infertility and reproductive health issues (Zeng et al., 2022). Research has established a link between PCOS and infertility (Meng et al., 2022; Kim et al., 2020; Zhan et al., 2023). The exact causes and mechanisms of PCOS are not yet fully understood, but it is believed to result from interplay between genetic and environmental factors (Escobar-Morreale, 2018). Women with PCOS often experience ovulation dysfunction, high androgen levels, and multiple small ovarian cysts, leading to symptoms such as irregular menstrual periods, excess hair growth, acne, infertility, and weight gain. Studies have shown that patients with PCOS have higher serum concentrations of PFOS compared to controls (Zhan et al., 2023). Additionally, high PFOS levels were associated with menstrual irregularities in both PCOS patients and controls, suggesting that PFAS may increase the risk of PCOS and related complications in women of reproductive age due to their endocrine-disrupting capabilities (Heffernan et al., 2018). A positive association was identified between mixture of 6:2 Cl-PFESA, HFPO-DA, PFOS, and PFDoA with an elevated odd of polycystic ovarian syndrome and PCOS-related infertility risk (Zhan et al., 2023). However, an inverse association was found between PFUdA levels and PCOS-related infertility, while no associations were observed for other PFAS compounds. These findings suggest that exposure to these compounds may play a role in the development and progression of PCOS and related infertility issues.

Exposure to certain PFAS has also been linked to an increased risk of ovarian cancer and endometriosis (Wang et al. 2017). The mean levels of PFOA, PFNA and PFOS were found to be higher in women who reported having endometriosis compared to women who did not (Campbell et al., 2016). The 2003-2006 NHANES study found a potential link between PFAS exposure and endometriosis in US women. Analyzing data from 753 women aged 20-50, researchers discovered that those with endometriosis had higher average levels of PFNA, PFOA, and PFOS compared to women without the condition (Campbell et al., 2016). However, the study's cross-sectional design, self-reported endometriosis diagnosis, and single-spot serum samples may limit its findings. Additionally, confounding variables such as age, BMI, parity, smoking status, and family history of endometriosis were identified. Despite these limitations, the study suggests a potential association between PFAS exposure and endometriosis, warranting further investigation. In a study of Chinese women with confirmed endometriosis, higher levels of PFBS in their blood were linked to a greater risk of infertility related to endometriosis, even in women who had never been pregnant or had no other gynecological conditions (Wang et al., 2017). Evidences has shown positive associations between exposure to PFAS in contaminated communities and the risk of developing ovarian cancer (Chang et al., 2023). Association has been found to exist between high exposure to PFOS and PFHxS (mostly used in firefighting foam) and increased risk for PCOS and uterine leiomyoma (Hammarstrand et al., 2021).

PFAS Exposure in Pregnancy and Impact on Birth Outcomes

Prenatal exposure to certain PFAS has been linked to reduced birth weight, with studies indicating a more pronounced effect in female newborns. Research by Wikström et al. (2020) revealed a significant correlation between maternal PFAS levels and lower birth weight, particularly in girls. Specifically, increased exposure to PFOS, PFOA, and PFHxS has been associated with reduced birth weight, with some studies suggesting a 50-100 gram reduction in birth weight per unit increase in maternal PFAS levels. This is concerning, as low birth weight (less than 2,500 grams) is linked to increased risks of infant mortality, respiratory distress, and long-term health consequences, including cardiovascular disease and metabolic disorders (Lin et al., 2007). Furthermore, PFAS exposure has also been implicated in preterm birth, which can exacerbate birth weight issues (Qin et al., 2023). While additional research is necessary to fully understand the relationship between PFAS and birth weight, existing evidence underscores the importance of minimizing PFAS exposure during pregnancy to protect fetal development and promote healthy birth outcomes (Qin et al., 2023). PFAS exposure has also been associated with neurodevelopmental toxicity, although the evidence from epidemiological studies on specific neurodevelopmental effects is inconsistent and requires further research. A study investigating the relationships between prenatal PFAS exposure and symptoms of attention-deficit/hyperactivity disorder (ADHD), cognitive functioning (language skills, estimated IQ, and working memory) in preschool children, and effect modification by child sex found some associations between PFAS and working memory, specifically negative relationships with nonverbal working memory and positive relationships with verbal working memory. However, these relationships were weak for both positive and negative, suggesting no clear association and the need for further studies to fully understand the effects of PFAS exposure on fetal development and neurodevelopmental outcomes (Skogheim et al., 2020).

Research has identified a level of association between prenatal exposure to PFOS and PFDA and an increased risk of preterm birth and miscarriage, with a direct linear relationship observed between the two (Gao et al., 2021; Chen et al., 2021; Green et al., 2021). Additionally, the presence of PFAS compounds has been detected in over 50 % of follicular fluid samples from Chinese women, highlighting their widespread presence (Kang et al., 2020). Exposure to PFAS has also been shown to alter placental cell function in mice and affect gene expression in liver and fat tissue in a sex-specific manner in offspring (Bangma et al., 2020; Szilagyi et al., 2020). A meta-analysis of 30 studies found associations between prenatal PFAS exposure and increased childhood body mass index (BMI) and waist circumference (WC), while childhood exposure was linked to reduced BMI (Frigerio et al., 2023). However, the evidence is not yet conclusive, and further research is necessary to validate these findings. The persistent presence of PFAS in the environment and human bodies, combined with their transfer from mother to child during pregnancy and breastfeeding, poses a potential threat to fetal growth and development (Gao et al., 2021; Padula et al., 2023).

Disruption of Ovarian Hormonal Regulation and Feedback Mechanisms by PFAS

The reproductive system is governed by an intricate hormonal process involving the pituitary gland, adrenal cortex, and gonads. At puberty, the hypothalamus initiates the release of gonadotropin-releasing hormone (GnRH), which stimulates the pituitary gland to produce and secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These gonadotropins play a vital role in regulating the function of the gonads (testes in males and ovaries in females), driving their development, maturation, and reproductive capacity (Marques et al., 2022). In both males and females, FSH and LH play crucial roles in regulating reproductive function. FSH promotes gametogenesis (sperm and egg production), while LH stimulates the gonads to produce sex hormones (testosterone and estrogen). As sex hormone levels rise, they exert a negative feedback effect on the hypothalamus, suppressing GnRH production and thereby regulating the reproductive axis. This feedback loop maintains a delicate balance in the reproductive system, preventing overstimulation.

Studies have demonstrated that PFAS, specifically PFOS accumulation in the hypothalamus can interfere with reproductive hormone regulation, leading to changes in sex hormone production and steroidogenesis (Starnes et al., 2022; Yang et al., 2022). Notably, studies have identified profound long-term effects, including reduced follicular estradiol levels in childless women (Barrett et al., 2015), impaired fetal reproductive development due to altered gonadotropin levels during pregnancy (Nian et al., 2020), increased risk of reproductive disorders, and altered gene expression in reproductive tissues. These changes have been shown to be persistent, even after exposure cessation, and are associated with adverse health outcomes, such as infertility, reduced fertility, pregnancy complications, endocrine disruption, and developmental issues. Specifically, the identified profound long-term effects include disrupted menstrual cycles, reduced fertility, increased risk of endometriosis and PCOS, birth defects, low birth weight, preterm birth, and increased cancer risk (Rickard et al., 2022).

Research has yielded inconsistent findings on the relationship between PFAS exposure and hormone levels, posing a challenge for understanding their impact on hormone regulation. In vitro studies have shown that PFOA and PFOS can exhibit both estrogenic and antiestrogenic properties, disrupting steroid hormone production and potentially affecting reproductive and endocrine systems. While some studies have found that PFOA and PFOS exhibit estrogenic properties, others have observed an inverse association between PFOS exposure and estradiol levels (Knox et al., 2011), suggesting that PFOS may both mimic and disrupt estrogenic activity. Cell-based assays have revealed that high concentrations of PFOA and PFOS can increase estrone and progesterone production (Behr et al., 2018), potentially leading to hormone imbalances. However, some studies have found no association between PFOA exposure and sex hormone levels, indicating a complex relationship that requires further investigation. Notably, PFOA has been shown to bind directly to progesterone, counteracting its effects on genes involved in embryo implantation and endometrial growth, suggesting a potential mechanism for reduced fertility and reproductive issues. Overall, the evidence suggests that PFAS exposure may have significant impacts on hormone regulation, but further research is needed to fully understand these effects.

The female reproductive tract is a complex system that relies heavily on hormonal feedback loops to regulate various physiological processes, including ovulation, menstruation, and pregnancy. These feedback loops are driven by changes in circulating hormone levels, which are precisely regulated by the hypothalamic-pituitary-gonadal axis. However, exposure to select PFAS has been shown to disrupt these delicate feedback loops, potentially leading to reproductive dysfunction. These PFAS can interfere with hormone regulation by altering hormone production, metabolism, or clearance, even if they do not directly activate receptors. For example, PFAS have been shown to:

- Inhibit the production of steroidogenic enzymes, leading to decreased hormone synthesis.
- Alter the expression of hormone receptors, affecting hormone signaling.
- Disrupt the balance of hormone-metabolizing enzymes, leading to changes in hormone clearance.
- Interact with hormone-binding proteins, affecting hormone transport and delivery.

These disruptions could have far-reaching consequences, including altered menstrual cyclicity and fertility, changes in ovulation and implantation, increased risk of pregnancy complications, and disrupted lactation and breast development. Moreover, PFAS exposure has been linked to changes in circulating hormone levels, including decreased estradiol and progesterone levels, increased androgen levels, and altered thyroid hormone levels.

Despite suggestions of a potential link between PFAS exposure and reproductive health concerns, scientific evidence remains inconclusive, with some studies indicating no significant correlation between these compounds and reproductive health. For instance, it was reported that there is inconclusive evidence for an association between PFAS and fetal growth (Säve-Söderbergh et al., 2024). Furthermore, many existing studies are limited by factors such as small sample sizes, incomplete exposure assessments, and methodological inconsistencies, which underscore the need for rigorous, well-designed investigations to definitively ascertain the relationship between PFAS exposure and reproductive health outcomes.

Table 1: Overview of epidemiological studies on PFAS and female reproductive health

Study year	Population	PFAS measured	Key findings
Barrett et al. (2015)	178 women between 25-35 years	PFOS	Positive association between PFOS and decreased production of estradiol in reproductive age women.
Nian et al. (2020)	752 mother-infant pairs	PFBS, PFHpA	Inverse association between PFBS and follicle stimulating hormone, and between PFHpA and Free Androgen Index. PFBS and PFHpA were associated with the disturbance of fetal gonadotropins and free androgen level.
Knox et al. (2019)	25 957 women between 18-65 years	PFOA, PFOS	Significant inverse association between PFOS and estradiol in perimenopausal and menopausal age groups but not between PFOA and estradiol.
Chen et al. (2021)	255 pregnant women	Five PFAS	No association between the PFAS and birth weight or head circumference was observed.
Lum et al. (2017)	501 couples	Seven PFAS	Serum levels of PFOA and PFDeA were associated with changes in menstrual cycle length.
Zhou et al. (2017)	950 women	Ten PFAS	PFOA and PFOS are associated with abnormal menstruation in humans.
Zhan et al. (2023)	366 women	Twenty three PFAS	Mixture of 6:2 Cl-PFESA, HFPO-DA, PFOS, and PFDoA was associated with an elevated odd of polycystic ovarian syndrome
Wikstrom et al. (2021)	78 women	Eight PFAS	PFOA was associated with first trimester miscarriage.
Säve-Söderbergh et al. (2024)	248 804	Four PFAS	PFOS was associated with increased risk of Large-for-gestational-age.

FUTURE DIRECTIONS IN PFAS-FEMALE REPRODUCTIVE HEALTH RESEARCH

Despite growing evidence linking PFAS to adverse female reproductive health outcomes, significant knowledge gaps remain. To better understand the complex relationships between PFAS exposure and female reproductive health, further research is necessary. Elucidating the molecular mechanisms underlying PFAS-induced reproductive toxicity is crucial. Investigating PFAS interactions with hormone receptors, gene expression, and epigenetic modifications will provide valuable insights. Additionally, developing more accurate methods to quantify PFAS exposure in humans, particularly during critical windows of vulnerability, is essential.

Large-scale, longitudinal studies examining PFAS exposure and reproductive health outcomes in diverse populations are needed to confirm associations and establish dose-response relationships. Research focusing on specific reproductive stages, such as follicular development, implantation, and pregnancy, will help identify critical periods of susceptibility. Also, investigating PFAS interactions with other endocrine-disrupting chemicals will provide a more comprehensive understanding of cumulative risks. Examining PFAS exposure during fetal development and early life stages will shed light on potential long-term reproductive health consequences.

To advance PFAS research and policy, collaboration between scientists, policymakers, and stakeholders is essential. Prioritizing research areas, translating findings into policy, and promoting public awareness would mitigate any potential harmful effects of PFAS on female reproductive health.

CONCLUSION

The persistence and bioaccumulation of PFAS, combined with their extensive use and release, may pose a significant threat to human and environmental health. There is growing concern that these "forever chemicals" could be polluting our environment and accumulating in humans, potentially impacting reproductive health and overall well-being. The ability of these substances to accumulate in the food chain raises concerns about long-term risks to human health and the environment, highlighting the need for continued monitoring. PFAS exposure raises concerns about female reproductive health, as they may disrupt hormone balance and fertility. This issue affects not only humans but also the broader ecosystem, with the potential to disrupt reproductive success in various species. To address this challenge, collaborative efforts from governments, industries, and individuals are necessary. A multidisciplinary approach can help manage PFAS usage, develop effective remediation technologies, and promote sustainable practices prioritizing human and environmental well-being.

LIST OF ABBREVIATIONS

6:2 FTOH	6:2 Fluorotelomer Alcohol Glucuronide
8:2 FTOH,	8:2 Fluorotelomer Alcohol Glucuronide
ADHD	Attention-Deficit/Hyperactivity Disorder
EDCs	Endocrine-Disrupting Chemicals
FSH	Follicle-Stimulating Hormone
GnRH	Gonadotropin-Releasing Hormone
hCG	Human Chorionic Gonadotropin Hormone
HPGA	Hypothalamic-Pituitary-Gonadal Axis
BMI	Body Mass Index
IPEN	International Pollutants Elimination Network
ITRC	Interstate Technology & Regulatory Council
IVF	In Vitro Fertilization
LH	Luteinizing Hormone
NHANES	National Health and Nutrition Examination Survey
NRDC	Natural Resources Defense Council
OECD	Organization for Economic Cooperation and Development
PCOS	Polycystic Ovary Syndrome
PFAS	Per- and Polyfluoroalkyl Substances
PFBS	Perfluorobutane Sulfonate
PFDA	Perfluorodecanoic Acid
PFHxS	Perfluorohexane Sulfonate
PFNA	Perfluorononanoic Acid
PFOA	Perfluorooctanoic Acid
PFOS	Perfluorooctane Sulfonate
PFDeA	Perfluorodecanoic Acid
PFTrDA	Perfluorotridecanoic Acid
PFUdA	Perfluoro-undecanoic Acid
Cl-PFESA	Chlorinated Polyfluoroalkyl Sulfonates
HFPO-DA	Hexafluoropropylene Oxide Dimer Acid
THDCs	Thyroid Disrupting Compounds
USEPA	United States Environmental Protection Agency
EU	European Union

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