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Per- and polyfluoroalkyl substances (PFAS) Induced Epigenetic Dysregulation in Endometriosis: A Mechanistic Review

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Abstract

Endometriosis is a chronic estrogen-dependent inflammatory disorder characterized by the ectopic growth of endometrial-like tissue and associated with pelvic pain, infertility, and impaired quality of life. Although its pathogenesis is multifactorial, increasing evidence suggests that environmental toxicants may contribute to disease development and progression through epigenetic mechanisms. Per- and polyfluoroalkyl substances (PFAS) are persistent environmental contaminants with recognized endocrine-disrupting, immunomodulatory, and oxidative stress inducing properties. Recent epidemiological and toxicological studies have reported associations between PFAS exposure and endometriosis, particularly in relation to disease severity and progression. This mechanistic review examines current evidence linking PFAS exposure to epigenetic dysregulation in endometriosis by integrating epidemiological, molecular, and toxicological findings. Particular emphasis is done on DNA methylation, histone modifications, chromatin remodeling, and non-coding RNA regulation as potential mediators of PFAS-induced reproductive toxicity. Available evidence suggests that PFAS-associated epigenetic alterations may disrupt steroid hormone signaling, immune surveillance, inflammatory pathways, angiogenesis, and fibrotic remodeling, thereby contributing to endometriosis pathophysiology. An integrative mechanistic framework is proposed to explain how chronic PFAS exposure may influence disease susceptibility and progression. Further investigation of these mechanisms may improve understanding of environmentally mediated reproductive toxicity and aid identification of potential epigenetic biomarkers in endometriosis.

Keywords: Endometriosis; PFAS; Epigenetic dysregulation; Endocrine disruption; DNA methylation; Reproductive toxicology.

1. Introduction

Endometriosis is a chronic gynecological disorder driven by an estrogen-dependent inflammatory process. It is characterized by the presence of endometrial-like tissue outside the uterine cavity, most commonly on the ovaries, pelvic peritoneum, uterosacral ligaments, and rectovaginal septum [1,2,3]. Clinically, the condition is associated with chronic pelvic pain, dysmenorrhea, dyspareunia, dysuria, and infertility, resulting in significant impairment in physical, psychological, and social well-being of affected women [4,5] (Figure 1).

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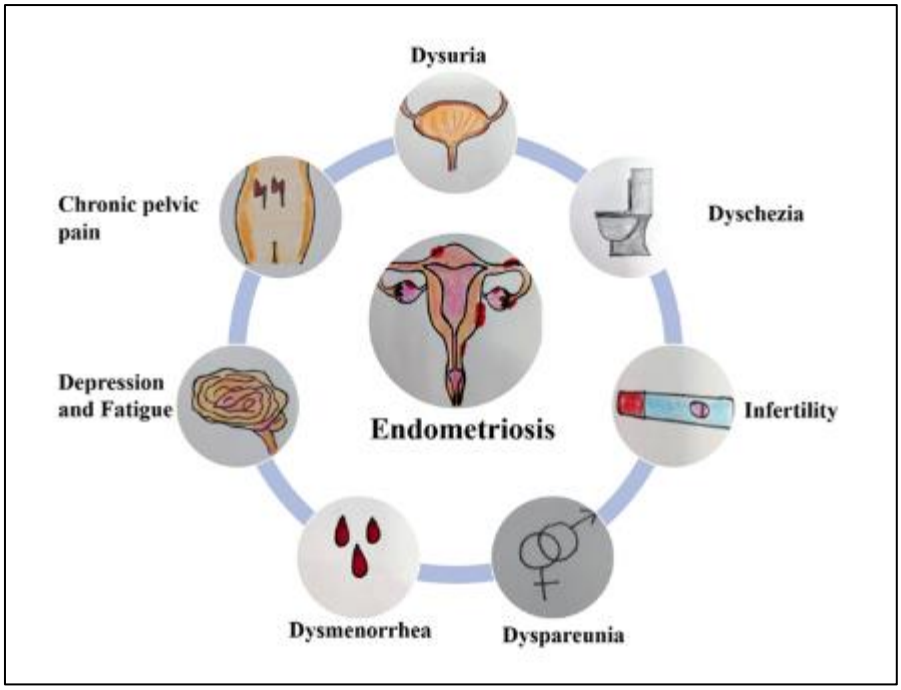

Figure 1 Common clinical manifestations and associated symptoms of endometriosis

The pathogenesis of endometriosis is multifactorial and incompletely understood [2,6]. A defining feature of endometriosis is its strong dependence on estrogen signaling coupled with resistance to progesterone action [1,3]. Increasing evidence suggests that many of these pathological features are, at least in part, regulated at the epigenetic level [1,7,8]. Epigenetic mechanisms including DNA methylation, histone modifications, chromatin remodeling, and non-coding RNA regulation are essential for normal endometrial function [7,9]. In endometriosis, this tightly regulated epigenetic landscape becomes disrupted [1,8].

Per- and polyfluoroalkyl substances (PFAS) are a large class of synthetic fluorinated chemicals characterized by highly stable carbon–fluorine bond that makes them environmentally persistent, leading to their global distribution in water, soil, food chains, and human biological samples [10,11,12]. Human exposure occurs primarily through contaminated drinking water, dietary intake, consumer products, and occupational settings [11,12]. From a toxicological perspective, PFAS are of concern due to their prolonged biological half-lives, bioavailability to multiple organ systems, and capacity to disrupt endocrine and immune function [11,13].

Several PFAS are now recognized as endocrine-disrupting chemicals capable of interfering with steroid hormone synthesis, receptor signaling, inflammatory pathways, and oxidative stress responses [13]. Recent epidemiological studies have begun to explore associations between PFAS exposure and gynecological disorders, including endometriosis and suggest that PFAS burden may be associated with disease presence, severity, or progression, particularly when mixture effects and tissue-specific exposure are considered [14,15]. Epigenetic mechanisms offer a biologically coherent framework through which PFAS exposure could exert lasting effects on hormonally sensitive tissues such as the endometrium. By altering DNA methylation, chromatin accessibility, or non-coding RNA expression, PFAS may contribute to reprogramming of gene networks governing steroid responsiveness, immune regulation, and inflammatory signaling, thereby increasing susceptibility to endometriosis or influencing disease progression [1,13,15].

2. Methodology

This review adopts a structured narrative review approach appropriate for integrating epidemiological, toxicological, and molecular evidence. A comprehensive literature search was conducted to identify relevant studies examining PFAS exposure, epigenetic mechanisms, and endometriosis using electronic databases including PubMed/MEDLINE, Scopus, Web of Science, Google Scholar (for supplementary sources), and ScienceDirect. In addition, authoritative reports and regulatory documents from organizations such as the Environment Agency and other environmental health bodies were consulted. Search terms including “per- and polyfluoroalkyl substances”; “endometriosis”; “epigenetics”; “endocrine disruption”; “inflammation” or “immune dysfunction” or “oxidative stress”; and “environmental exposure” were applied both individually and in combination using Boolean operators (AND, OR) to ensure comprehensive retrieval of relevant

studies across disciplines. Inclusion criteria comprised studies that examined PFAS exposure in relation to endometriosis, epigenetic mechanisms, or broader reproductive and endocrine outcomes. Both human studies and experimental models, including animal and *in vitro* systems were considered. Only peer-reviewed studies providing original findings or significant mechanistic insight were included.

3. Epigenetic Dysregulation in Endometriosis

3.1. Per- and polyfluoroalkyl substances and Reproductive toxicology

Per- and polyfluoroalkyl substances (PFAS) are synthetic organofluorine compounds characterized by the presence of at least one fully fluorinated carbon atom conferring exceptional physicochemical stability and resistance to thermal, chemical, and biological degradation [10,16]. These chemical properties have resulted in their widespread application in consumer and industrial products, including non-stick cookware, water-repellent textiles, food packaging, surface coatings, and aqueous film-forming foams (AFFFs) used for firefighting [10,12]. Importantly these properties also underlie their environmental persistence. Their resistance to degradation allows them to persist for decades in environmental matrices, including surface water, groundwater, soil, sediments, and biota [16,17,18]. Human exposure to PFAS occurs through multiple routes, primarily via ingestion of contaminated water and food. Consumption of contaminated drinking water and food items particularly fish, seafood, and animal products constitutes a major source of PFAS intake [17,18]. Additional exposure pathways include occupational exposure, inhalation of indoor dust, and dermal contact with PFAS-treated materials [12,17].

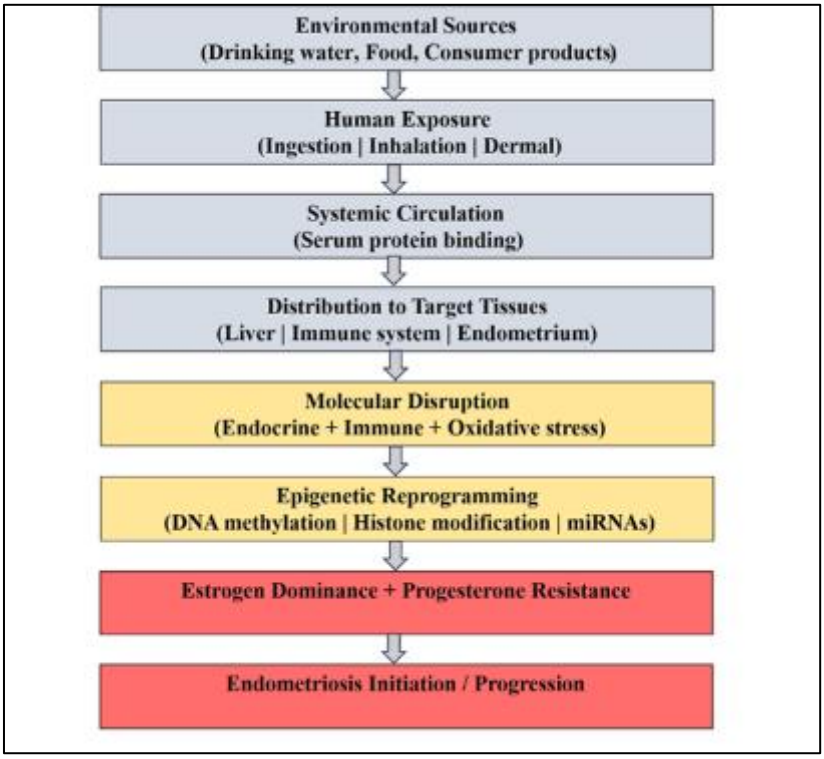

Figure 2 Proposed mechanistic pathway linking environmental PFAS exposure to endometriosis initiation and progression

A defining toxicological feature of PFAS is their preferential binding to serum proteins, such as albumin and liver fatty acid–binding proteins, enabling systemic distribution to organs including the liver, kidney, immune system, and reproductive tissues [10,18]. Several legacy PFAS exhibit prolonged biological persistence in humans, with reported half-lives ranging from approximately 2 to 8 years for compounds such as PFOA, PFOS, and PFHxS after exposure cessation [11]. Elimination kinetics may vary according to compound characteristics and biological factors, including sex-related differences in clearance [11]. Experimental and epidemiological studies indicate that PFAS interfere with hormone synthesis, transport, receptor signaling, and metabolism, particularly within estrogenic and progestogenic pathways supporting the classification of PFAS as endocrine-disrupting chemicals [13]. PFAS have been shown to interact with nuclear receptors, including peroxisome proliferator-activated receptors (PPARs), and to modulate

steroidogenic enzyme expression, thereby disrupting hormonal homeostasis [13]. In female reproductive systems, PFAS exposure has been associated with altered circulating sex hormone levels, impaired ovarian function, menstrual irregularities, and reduced fecundability. These effects are particularly significant as they occur at environmentally relevant exposure levels and may be amplified by chronic bioaccumulation [11,13,17]. Such endocrine and reproductive perturbations are directly relevant to hormonally regulated gynecological disorders including endometriosis [14]. The proposed mechanistic pathway linking PFAS exposure to endocrine disruption, epigenetic dysregulation, and endometriosis progression is illustrated(Figure 2).

3.2. Epidemiological Evidence

Given the chronic, hormone-dependent nature of endometriosis and the persistence of per- and polyfluoroalkyl substances (PFAS) in human tissues, population-based investigations provide critical insight into whether long-term PFAS exposure influences disease susceptibility, severity, or progression [2,5,11,19]. Studies published between 2023 and 2025 have begun to address earlier methodological limitations, with recent meta-analytic evidence further supporting emerging associations [13,14,15,20,21].

A large case–control study conducted among reproductive-aged women measured serum concentrations of multiple PFAS and identified significantly higher levels of selected compounds—including perfluorooctane sulfonate (PFOS), perfluorononanoic acid (PFNA), and perfluorohexane sulfonate (PFHxS)—among women with surgically confirmed

endometriosis compared to controls [20]. Importantly, these associations persisted after adjustment for age, body mass index, parity, and other potential confounders. Similarly, the Endometriosis and Environmental Exposure (ENDEA) study conducted in Spain reported elevated total PFAS burden among women with endometriosis, with particularly strong associations observed for branched PFOS isomers [14].

The Invest-Endo study quantified PFAS concentrations in eutopic endometrial tissue from women with and without endometriosis and detected PFAS in nearly all samples analyzed [15]. This tissue-level evidence is particularly important because it reduces exposure misclassification associated with serum-only measurements and supports biological relevance at the target organ. These findings suggest that PFAS may contribute to lesion persistence, inflammation, and fibrotic remodeling in advanced disease stages [13,15]. Traditional epidemiological analyses often focus on individual PFAS; however, humans are exposed to complex mixtures. Recent studies have employed mixture-based statistical and systems-toxicology approaches to address this limitation. A 2025 integrative study combining epidemiological data with network toxicology and molecular docking analyses demonstrated that PFAS mixtures were associated with endometriosis risk through convergent endocrine and inflammatory pathways [22]. This approach identified key molecular targets involved in estrogen signaling, immune activation, and oxidative stress pathways already implicated in endometriosis pathogenesis. By integrating exposure data with biological pathway analysis, such studies strengthen causal plausibility and help bridge the gap between population-level associations and mechanistic understanding. Collectively, current epidemiological evidence suggests a potential association between PFAS exposure and endometriosis, particularly in relation to disease severity and progression. Strengths of recent studies include improved exposure assessment, consideration of PFAS mixtures, isomer-specific analyses, and incorporation of tissue-level measurements [14,15,20,21,22].

However, several important limitations remain. Many studies are cross-sectional, limiting temporal inference. Diagnostic misclassification persists due to variability in clinical confirmation. Confounding by reproductive history, hormonal treatments, and co-exposures is difficult to fully address. Additionally, most studies focus on legacy PFAS, with limited data on emerging replacement compounds [14,15,22].

3.3. Epigenetic Mechanisms

Epigenetic mechanisms including, DNA methylation and hydroxymethylation, histone post-translational modifications, chromatin remodeling, and non-coding RNA regulation, govern cell-type–specific gene expression and enable dynamic responses to hormonal and inflammatory cues [7,9]. Because these modifications can be stable yet reversible, they are particularly relevant to chronic diseases characterized by persistent dysregulation rather than irreversible genetic mutations. Endometriosis is increasingly recognized as a disease marked by stable aberrations in gene expression that are maintained across menstrual cycles and persist even after removal from the ectopic environment [1,8,23]. In parallel, per- and polyfluoroalkyl substances (PFAS) are characterized by prolonged biological half-lives and continuous internal exposure, creating conditions conducive to epigenetic reprogramming [11,24]. The convergence of these features positions epigenetic dysregulation as a plausible mechanistic link between PFAS exposure and endometriosis [11,24].

3.4. DNA Methylation and Hydroxymethylation

DNA methylation is one of the most extensively studied epigenetic mechanisms in the context of environmental exposure. Multiple human and experimental studies have demonstrated that PFAS exposure is associated with differential DNA methylation across the genome, affecting genes involved in endocrine signaling, immune regulation, metabolism, and inflammatory pathways [13,24]. These alterations are thought to arise through disruption of DNA methyltransferase (DNMT) activity, ten-eleven translocation (TET) enzymes, or availability of methyl donors. Human cohort studies summarized in recent reviews indicate that PFAS-associated methylation changes are detectable at environmentally relevant exposure levels and may persist over time, supporting their potential role in long-term disease susceptibility [24]. Importantly, several of the pathways affected by PFAS-related methylation changes such as estrogen receptor signaling, cytokine production, and oxidative stress response overlap with those implicated in endometriosis pathophysiology [1,8]. This convergence strengthens the mechanistic link between PFAS exposure and endometriosis, even in the absence of direct epigenomic profiling of endometriotic lesions in exposed populations.

3.5. Histone Modifications and Chromatin Remodeling

Histone modifications represent another critical layer of epigenetic regulation susceptible to environmental perturbation. Experimental evidence summarized in PFAS toxicology reviews suggests that PFAS exposure can alter histone acetylation and methylation patterns, thereby influencing chromatin accessibility and transcriptional activity [13]. Such changes may occur through modulation of histone-modifying enzymes or secondary effects of oxidative stress and inflammatory signaling. In endometriosis, altered histone modification patterns have been implicated in dysregulated expression of genes involved in steroid hormone responsiveness, inflammation, and extracellular matrix remodeling [1]. While direct evidence linking PFAS exposure to histone modifications in endometrial tissue remains limited, the capacity of PFAS to influence chromatin dynamics in other biological systems supports the plausibility of similar effects in hormonally responsive reproductive tissues.

3.6. Non-Coding RNAs

Non-coding RNAs, particularly microRNAs (miRNAs), play essential roles in post-transcriptional gene regulation and are increasingly recognized as environmentally responsive epigenetic regulators. Reviews of PFAS toxicology indicate that PFAS exposure can modify miRNA expression profiles, affecting pathways related to inflammation, endocrine signaling, cell proliferation, and apoptosis [13,24].

In endometriosis, dysregulated miRNA expression has been documented in both eutopic and ectopic endometrial tissues and is thought to contribute to progesterone resistance, estrogen dominance, and immune dysfunction [1]. Although direct studies examining PFAS-induced miRNA changes in endometrial tissue are scarce, the overlap in affected biological pathways suggests that altered non-coding RNA regulation may represent an important intermediary mechanism linking PFAS exposure to disease-relevant molecular phenotypes.

3.7. Human Evidence and Mechanistic Implications

Human epidemiological and biomonitoring studies provide critical support for PFAS-induced epigenetic dysregulation. Epigenome-wide association studies (EWAS) summarized in recent reviews have identified PFAS-associated differential methylation at loci involved in hormone signaling, immune response, and metabolic regulation [24]. Notably, these studies demonstrate that epigenetic alterations can be detected in peripheral tissues, supporting the concept of systemic epigenetic reprogramming.

While most available data derive from blood-based analyses rather than reproductive tissues, tissue-based PFAS measurements in endometriosis studies provide complementary evidence of target-organ exposure [15]. The detection of PFAS within eutopic endometrial tissue underscores the biological feasibility of local epigenetic effects and highlights the need for future studies integrating exposure assessment with tissue-specific epigenomic profiling.

Because epigenetic changes can be stable yet environmentally responsive, PFAS-induced epigenetic dysregulation provides a mechanistic explanation for how long-term, low-dose exposure could influence disease susceptibility or progression without direct genotoxicity. This framework also helps reconcile inconsistent epidemiological findings by suggesting that PFAS effects may depend on timing, duration, and cumulative exposure rather than single-point measurements.

3.8. Integrative Mechanistic Model

Complex chronic diseases such as endometriosis cannot be explained by single-factor causation. Instead, disease initiation and progression arise from interactions among hormonal regulation, immune function, inflammatory signaling, tissue remodeling, and long-term molecular reprogramming [1,2,3]. Epidemiological evidence linking per- and polyfluoroalkyl substances (PFAS) to endometriosis, although heterogeneous, suggests that persistent environmental exposures may modulate these interconnected biological systems [5,14,15]. An integrative mechanistic framework helps explain how chronic low-dose PFAS exposure may produce sustained disease-relevant alterations. Epigenetic regulation provides a biologically coherent intermediary, capable of integrating environmental signals and producing stable yet reversible changes in gene expression that align with known features of endometriosis pathophysiology [1,3,13].

PFAS are characterized by environmental persistence, prolonged biological half-lives, and continuous internal exposure once absorbed [11]. Unlike transient endocrine disruptors, PFAS remain in circulation for years, leading to sustained interaction with hormonally sensitive tissues, including the endometrium [11,14]. Tissue-level detection of PFAS in eutopic endometrial samples provides direct evidence that these compounds reach biologically relevant target sites [15]. Chronic PFAS exposure exerts molecular stress through endocrine disruption, immune modulation, oxidative stress induction, and receptor-mediated signaling perturbation [13,24]. These processes create cellular environments conducive to epigenetic remodeling, particularly in tissues undergoing cyclical proliferation and differentiation such as the endometrium [1,3,24].

3.9. Hormonal Dysregulation

One of the central features of endometriosis is dysregulated estrogen and progesterone signaling. Epigenetic modifications regulate the expression and activity of estrogen receptors, progesterone receptors, and enzymes involved in local estrogen biosynthesis [1]. PFAS-induced alterations in DNA methylation and chromatin accessibility may disrupt this regulatory balance, leading to estrogen dominance and progesterone resistance. Within endometrial tissue, these epigenetic alterations may impair progesterone responsiveness, enhance estrogen-driven proliferation, and facilitate lesion persistence [1,2,3].

3.10. Immune Dysfunction and Inflammation

Immune dysfunction and chronic inflammation are essential components of endometriosis pathophysiology. Epigenetic regulation governs the expression of cytokines, chemokines, immune receptors, and signaling mediators that determine immune surveillance and inflammatory tone [2,3]. Impaired immune surveillance may allow ectopic endometrial cells to evade clearance by natural killer cells and macrophages, thereby facilitating lesion persistence and chronic inflammation [25,26]. PFAS exposure has been shown to influence immune-related gene expression and inflammatory pathways through epigenetic mechanisms, including altered DNA methylation and non-coding RNA regulation [13].

PFAS-induced epigenetic reprogramming may reduce immune clearance of ectopic endometrial cells by suppressing cytotoxic responses while simultaneously promoting a pro-inflammatory microenvironment that supports lesion survival [3,13]. These inflammatory processes are also closely linked to nociceptive sensitization, which contributes to the chronic pain phenotype commonly associated with endometriosis [27,28,29]. This dual effect aligns with epidemiological observations linking PFAS burden to disease severity rather than simple disease presence [15].

3.11. Angiogenesis, Fibrosis, and Tissue Remodeling

Successful establishment of endometriotic lesions requires angiogenesis, extracellular matrix remodeling, and fibrotic transformation. These processes are tightly regulated by epigenetic mechanisms controlling expression of angiogenic factors, matrix metalloproteinases and fibrogenic mediators [3,24,30]. PFAS-associated epigenetic alterations affecting oxidative stress and growth factor signaling may indirectly promote angiogenesis and fibrosis by sustaining inflammatory signaling and altering chromatin accessibility of key regulatory genes [13,24]. In advanced-stage disease, cumulative epigenetic reprogramming may therefore contribute to lesion vascularization, fibrotic stiffening, and resistance to regression, consistent with tissue-level PFAS findings [15].

The integrative PFAS → epigenome → endometriosis model reconciles several observations across evidence domains. Epidemiological studies demonstrate associations between PFAS exposure and endometriosis severity, while tissue-based analyses confirm direct exposure of endometrial tissue [14,15]. Concurrently, mechanistic studies show that PFAS can induce epigenetic alterations affecting endocrine, immune, and inflammatory pathways relevant to disease biology [13,24]. Rather than acting as direct initiators, PFAS may function as disease modifiers influencing susceptibility, progression, and therapeutic response through long-term epigenetic reprogramming [24,21]. This model also explains

variability across studies, as epigenetic effects are influenced by exposure timing, duration, mixture composition, and individual susceptibility [5,13] (Figure 3).

Taken together, current evidence supports a conceptual framework in which chronic PFAS exposure induces epigenetic dysregulation in hormonally responsive and immune-regulated pathways within the endometrium [13,24]. These epigenetic alterations disrupt steroid hormone signaling, impair immune clearance, sustain inflammation, and promote angiogenesis and fibrosis, collectively contributing to the development and progression of endometriosis. This integrative model provides a mechanistic basis for future studies aimed at clarifying causal relationships and identifying potential epigenetic biomarkers or therapeutic targets. It also highlights the importance of considering environmental exposures within the broader biological context of endometriosis.

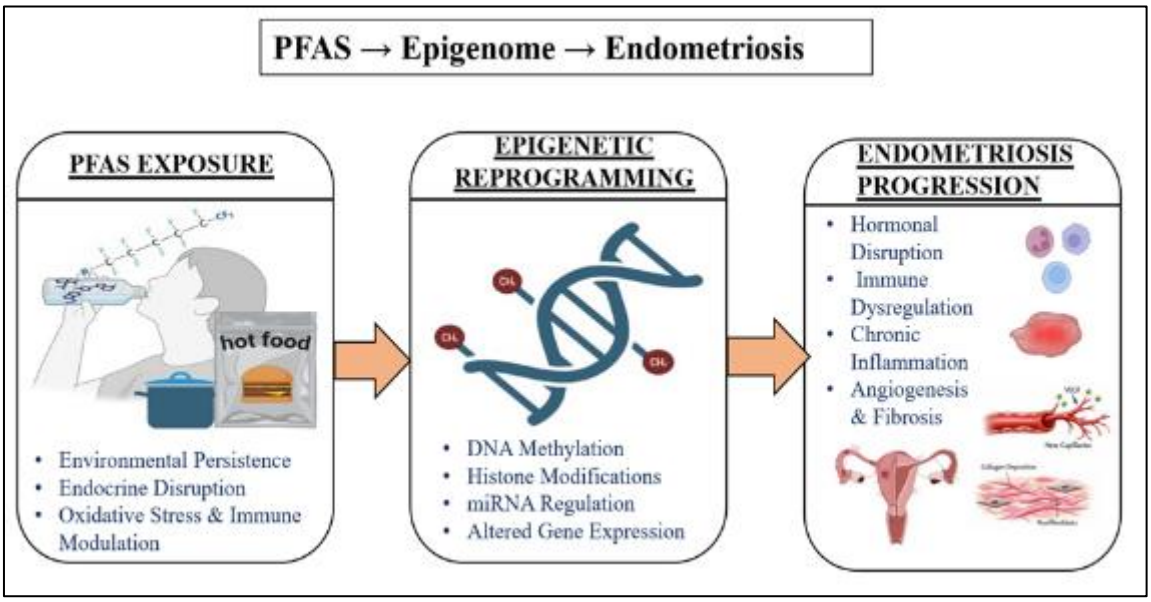

Figure 3 Conceptual framework illustrating the role of PFAS-induced epigenetic reprogramming in endometriosis progression

4. Discussion

This review synthesizes evidence supporting the hypothesis that per- and polyfluoroalkyl substances (PFAS) may contribute to endometriosis through epigenetic dysregulation [24]. PFAS are environmentally persistent chemicals with long biological half-lives, widespread human exposure, and demonstrated endocrine-disrupting and immunomodulatory properties [10,11,13]. Epidemiological studies reviewed herein indicate that PFAS exposure is associated with endometriosis, particularly in relation to disease severity and progression, while tissue-based investigations confirm that PFAS reach biologically relevant reproductive compartments [14,15]. Although heterogeneity across studies limits definitive causal conclusions, consistency in biological pathways implicated strengthens the overall plausibility of these associations.

Mechanistic evidence further supports an epigenetic link between PFAS exposure and endometriosis-relevant pathways [24]. PFAS-associated alterations in DNA methylation, chromatin regulation, and non-coding RNA expression have been documented in human and experimental systems, affecting genes involved in steroid hormone signaling, immune regulation, oxidative stress, and inflammatory responses [13,24]. These pathways overlap substantially with those known to be dysregulated in endometriosis, providing a coherent mechanistic bridge between exposure and phenotype [1,2,3]. Importantly, epigenetic modifications offer a biologically credible explanation for how chronic, low-dose PFAS exposure could exert lasting effects without direct genotoxicity.

The integrative mechanistic model presented in this review conceptualizes PFAS not as singular causal agents but as disease modifiers capable of reprogramming epigenetic landscapes in hormonally sensitive tissues [21]. Through sustained epigenetic perturbation, PFAS may amplify estrogen dominance, reinforce progesterone resistance, impair immune surveillance, and promote inflammatory and angiogenic processes that support lesion persistence [1]. This model also helps reconcile inconsistencies in epidemiological findings by emphasizing exposure timing, cumulative burden, chemical mixtures, and individual susceptibility. Despite increasing mechanistic and epidemiological evidence,

important research gaps remain. Future longitudinal and tissue-specific studies integrating precise exposure assessment with epigenomic and functional analyses are needed to strengthen causal inference and improve understanding of PFAS-related reproductive toxicity [5,22,24].

5. Conclusion

In conclusion, current evidence supports the biological plausibility of PFAS-induced epigenetic dysregulation as a contributing factor in endometriosis. While definitive causality cannot yet be established, the convergence of epidemiological, toxicological, and epigenetic data underscores the importance of considering persistent environmental exposures in the broader biological context of endometriosis. Advancing this field will not only enhance understanding of disease mechanisms but also inform preventive strategies and risk assessment frameworks aimed at protecting women's reproductive health.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors have no any conflict of interest for publishing this article.

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