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REVIEW

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Impact of endocrine disrupting chemicals (EDCs) on epigenetic regulation in the uterus: a narrative review

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Abstract

Endocrine disrupting chemicals (EDCs) are ubiquitous in the environment and have been shown to interfere with the endocrine system, leading to adverse effects on reproductive health. In females, EDC exposure has been linked to menstrual irregularities, infertility, and pregnancy complications. Epigenetic regulation, which involves modifications to DNA and histones that do not alter the underlying genetic code, plays a crucial role in female reproduction. EDCs have been shown to disrupt epigenetic mechanisms, leading to changes in gene expression that can have long-term effects on reproductive outcomes. Several EDCs, including bisphenol A (BPA) and phthalates, dioxins, and polychlorinated biphenyls (PCBs), have been shown to alter DNA methylation patterns and histone modifications in female reproductive tissues. These changes can lead to altered expression of genes involved in ovarian function, implantation, and placental development. Here, we integrate epidemiological and experimental evidence from the last 20 years to profile the types of diseases that EDCs trigger in the female reproductive system in relation to the uterus, and the corresponding molecular mechanisms that have been studied. In addition, this review will outline the state of knowledge of EDC epigenetic regulation in the uterus and how it impacts reproductive health, as well as identify areas for future research.

Keywords Endocrine disrupting chemicals, Endometrial hyperplasia, Endometriosis, Uterus, Epigenetic regulation

Introduction

Found in many household and industrial products, endocrine disrupting chemicals or compounds (EDCs) are chemicals that, at certain doses, can interfere with the endocrine system in mammals. These disruptions can cause cancerous tumors, birth defects, and other developmental disorders. Any system in the body controlled by hormones can be affected by them. Female disorders are closely related to hormone imbalance, so endocrine disrupting chemicals can exert a negative impact on female reproduction. There have been several articles reviewing the relationship between EDCs and ovarian function [1–5], but fewer on their relationship to uterine function. Accumulating evidence has suggested that

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EDCs can induce epigenetic modulations [2, 6–14], leading to gene expression changes and potentially causing female reproductive disorders, including atypical endometrial hyperplasia, female infertility, endometriosis, uterine fibroids, and recurrent pregnancy loss [8, 12, 15–17]. Many of the environmental endocrine disruptors have been shown to be involved in epigenetic regulation, including Bisphenol A (BPA), phthalates, dioxins, polychlorinated biphenyls (PCBs), and diethylstilbestrol (DES). There are three main mechanisms of epigenetic regulation triggered by environmental endocrine disruptors in utero-related female reproductive diseases: DNA methylation, histone modifications, and microRNA alterations. The signaling pathways involved in utero-related epigenetic regulation include but are not limited to the PI3K/AKT signaling pathway, the interaction between WDR5 and TET2, and the imprinted genes ASCL2 and HOXA10 [8, 16–19]. Interestingly, for the study of the same imprinted gene, even for the same environmental endocrine disruptor, epigenetic regulation may go in diametrically opposite directions [19–21]. This is due to the complex biological activity of different EDCs that is related to the substance, dose, target, exposure window, and species-specific effects. Therefore, much research is required to fully understand the role of these ubiquitous toxins in women's reproductive health. This article aims to review the current state of knowledge of how different EDCs contribute to the aetiology of uterine disease through epigenetic modifications. Evidence is taken from human epidemiological studies, in vitro cell based studies and in vivo animal studies.

Methods

Original articles were selected from PubMed searches performed using the search terms 'endocrine disrupting chemicals AND female reproduction'; 'endocrine disrupting chemicals AND uterus', 'endocrine disrupting chemicals AND endometrium'. The inclusion criteria for publications were: English language, time of publication was between January 2005 and January 2024, original studies. The exclusion criteria were polycystic ovary syndrome, ovarian tumors and sexual abnormalities. This was followed by a full-text reading of the literature that met the inclusion criteria. Then, according to the EDCs and eligible reproductive disorders, they were then searched for epigenetic regulation. While reading the articles, the following information was extracted: experimental design, types of EDCs involved, main experimental results, uterine disorders involved, and epigenetic modulation mechanisms. The data is summarized in tables, categorizing them into human epidemiology studies (Table 1), in vivo animal studies (Table 2) and in vitro cell-based studies (Table 3).

Female reproductive disorders

The female reproductive system is a complex and delicate system impacted by various hormones and environmental factors. Female reproductive disorders are becoming increasingly common, and environmental factors are believed to play a significant role in their development. One set of factors are the EDCs, which are known to interfere with the normal functioning of hormones in the body. EDC exposure increases the risk of tumorigenesis, especially in organs susceptible to endocrine regulation [22], including the uterus. The endometrium undergoes periodic patterns of endocrine and immune signaling that regulate its growth and function during childbearing years and is particularly sensitive to these endocrine disrupting chemicals [23]. EDCs can affect genes' epigenetic regulation, leading to gene expression changes and potentially causing female reproductive disorders. The majority of focus has been on EDCs and puberty abnormalities and obesity, female ovarian dysfunction, or male infertility. In the current review we will focus on female reproductive disorders associated with the uterus.

Endocrine disrupting chemicals (EDCs)

The Endocrine Society has declared two Scientific Statements on environmental endocrine disrupting chemicals, the second of which was in 2015 and contained a comprehensive summary of seven areas: obesity and diabetes, female reproduction, male reproduction, hormone-sensitive tumors in females, the prostate gland, thyroid, and the brain, especially neurodevelopment, and neuroendocrine systems [24]. EDCs are exogenous or synthetic chemicals that can interfere with the endocrine system by altering the synthesis, secretion, transportation, metabolism, or action of endogenous hormones [25]. More than 1480 EDCs are now known and they can be found in various daily products such as plastics, detergents, flame retardants, pesticides, and personal care products [26, 27]. Their exposure modes in humans mainly include digestion, inhalation and skin contact [28]. Human exposure to EDCs begins as early as in utero, and these chemicals have been shown to cross the placenta to reach the fetus [29].

The degree of toxicity of EDCs largely depends on the stage at which a person is exposed to them. During the window of vulnerability, the prenatal or neonatal period, small quantities of EDC could harm the human body. Since the embryo and fetus are the most vulnerable to harsh changes in the external environment, the deleterious effect won't disappear after the EDC is eliminated. On the contrary, the disruptions induced by EDCs could probably be long-lasting until adulthood and exhibit a trans-generational effect [11]. This is consistent with Barker's hypothesis, which is well-established as the developmental origins of health and disease

Table 1 Relationship between EDC exposure and reproductive tissues in epidemiological studies

Study design	EDC	Results	Uterine disorder	Epigenetic modulation	References
Extensive prospective study	DES	All five black women reported exposure to DES had uterine fibroids. Of the white women who reported prenatal DES exposure, 76% had leiomyomas.	Uterine fibroids	Uninvestigated	[53]
Case-control study	PCDD, PCDF, dioxin-like PCB	A 10 pg increase in total TEQ was associated with a significant increased risk of deep endometriosis nodules. There was also an increased total TEQ level, and the risk of dioxin use alone in peritoneal endometriosis.	Endometriosis	Uninvestigated	[71]
Case-control study	NDL-PCBs and DL-PCBs, p,p'-DDE, HCB	DL-PCB-118, NDL-PCB-138, NDL-PCB-153, NDL-PCB-170, and the sum of DL-PCB and NDL-PCB are at increased risk of endometriosis.	Endometriosis	Uninvestigated	[74]
Case-control study	Noncoplanar PCBs	PCB concentrations and estrogen concentrations were not associated with endometriosis risk.	Endometriosis	Uninvestigated	[103]
Prospective case-control study	MEHP and DEHP	Concentrations of MEHP and DEHP were significantly higher in patients with advanced endometriosis.	Endometriosis	Uninvestigated	[69]
Matched cohort	BPA and 14 phthalate metabolites	Six phthalate metabolites were significantly associated with an approximately twofold increase in the probability of endometriosis diagnosis.	Endometriosis	Uninvestigated	[104]
Extensive prospective study (Nurses' Health Study II)	DES	During 1,273,342 person-years of follow-up, there were 11,831 UL events. Women prenatally exposed to DES have higher Incidence of UL compared to non-exposed ones especially in the first trimester.	Uterine fibroids	Uninvestigated	[54]
Case-control study	BPA	A statistically significant positive correlation was observed between total urine BPA concentrations and non-ovarian pelvic endometriosis, but not ovarian endometriosis.	Endometriosis	Uninvestigated	[68]
Case-control study	BPA and phthalates	The relationship between endometriosis and all grouped metabolites was not statistically significant. However, miBP concentrations due to endometriosis were relatively high, with an odds ratio of 1.929.	Endometriosis	Uninvestigated	[70]
Cohort Follow-up Study	DES	DES-exposed third generation women are at increased risk of menstrual irregularities and amenorrhea compared with unexposed individuals. Follow-up data also suggest a link to preterm birth.	Irregular menstrual cycles, amenorrhea, and premature birth	Uninvestigated	[91]
Case-control study	BPA	Creatinine-adjusted urinary BPA concentration was positively correlated with serum MMP2, MMP9 levels and peritoneal endometriosis risk.	Endometriosis	Uninvestigated	[80]
Cohort Study	PFAS	Exposed group of the cohort had significantly higher age at menarche and frequency of menstrual irregularities.	Irregular menstrual cycles	Uninvestigated	[92]
Cross-sectional study	Parabens (MP, EP, PP, and BP), BP-3, BPA, and TCS	Of total 789 individuals included in the study, 14% had infertility. MP and PP were detected in 99% of urine samples, BP in 46%, EP and BP-3 in 96%, BPA in 94% and TCS in 73%.	Infertility	Uninvestigated	[87]
Retrospective observational analysis	DES	12 cases of uterine malformations (3 aplastic uterus (MRKHS), 3 uterine doubling, and 6 bicornuate uterus) were observed.	Uterine defects	Uninvestigated	[88]
Case-control study	OPEs, APs, and phthalates	The exposure to OPEs, APs, and phthalates was associated with an elevated risk of uterine fibroids in premenopausal women.	Uterine fibroids	Uninvestigated	[50]
Cohort Study	Sixty-three serum chemicals and three blood metals	Preconception PBDE28 and cadmium concentrations in women were positively correlated with hCG pregnancy loss in a group of couples from the general population who were trying to conceive.	HCG pregnancy loss	Uninvestigated	[105]
Cross-sectional study	Phthalates	Women with recurrent miscarriage and idiopathic infertility had significantly higher MEP mean values than women with other infertility factors. Women with tubal factors such as infertility, RPL, and endocrine dysfunction have higher DEHP values.	Recurrent miscarriage, infertility	Uninvestigated	[106]

Table 1 (continued)

Study design	EDC	Results	Uterine disorder	Epigenetic modulation	References
Case-control study	Six bisphenol analogues (BPA, BPAF, BPAP, BPB, BPP and BPS)	Mixed exposure to the six bisphenol analogues was positively associated with URM risk, mainly driven by BPAP (60.1%), BPAF (25.1%), and BPA (14.8%).	Unexplained recurrent miscarriage	Uninvestigated	[107]
Case-control study	Phthalates	URSA was associated with higher concentrations of mEHHP, mEHP and mEP, DEHP, and lower concentrations of miBP.	Unexplained recurrent spontaneous abortion	Uninvestigated	[108]
Case-control study	PCB169	Blood concentrations of PCB169 were significantly relevant to miR-191 expression in pregnant women who underwent therapeutic abortion due to fetal malformations in PCB-contaminated regions.	Uninvestigated	miR-191 alteration	[109]
Cohort Study	8 phenols and 11 phthalate metabolites	A significant decrease in H19 methylation is related to high combined levels of phthalate metabolites and low molecular weight (LMW) phthalate metabolites.	Uninvestigated	DNA methylation	[110]
Harvard Epigenetic Birth Cohort and the Predictors of Preeclampsia Study	8 phenols and 11 phthalate metabolites	There were three miRNAs that were significantly related to phenol or phthalate levels (miR-185, miR-142-3p, miR-15a-5p). Their potential mRNA targets were associated with several biological pathways, including the modulation of protein serine/threonine kinase activity.	preeclampsia	microRNA alterations	[111]

(DOHaD) [30]. It emphasizes the role of prenatal and perinatal exposure to environmental factors in determining the development of human diseases in adulthood and included an emphasis on epigenetic causes of adult chronic diseases [31–33].

"Low dose" is a critical feature of EDCs, which can be interpreted in 3 ways: (1) below the dose used in traditional toxicology studies, i.e. below the level of unobserved adverse reactions (NOAEL) or low levels of observed adverse effects; (2) the dose is within the typical range of human exposure, or (3) animal dosage is equal to the circulating concentration in the human body. The "low dose" characteristic of EDCs is partly due to the high affinity of hormone receptors. Another reason is that they help endogenous hormones amplify their biological effects [34]. In addition, even if individual compounds are concentrated below the supervised dose, cumulative exposure to the compound mixture may be associated with adverse health outcomes [35–37]. Unlike human hormones, which exhibit a linear dosage response, the dose-response patterns of EDCs are complicated, often showing a nonmonotonic dose-responsive curve that includes a U-shape and an inverted U-shape [34, 38, 39]. Even the same EDC, take BPA for example, has a variety of modes of action, and can present opposite effects on cell proliferation depending on dose and target cell type [34, 40].

EDCs and reproductive disorders

In female reproduction, EDCs have been linked to a range of negative outcomes related to the uterus, including endometrial hyperplasia, uterine fibroids, endometriosis, infertility, and pregnancy loss. The epidemiological, animal and cell culture evidence for the role of different EDCs in uterine reproductive disorders is summarized in Tables 1, 2 and 3 respectively.

EDCs and endometrial hyperplasia

Since 1980, there has been a continued decline in fertility and increasing rate of excess female body weight which may have contributed to an increased incidence in uterine cancer in previous years, although the incidence appears to have remained relatively stable in recent years [41]. Compared to the global cancer statistics in 2020 [42], uterine cancer rose from sixth to fourth place in the ranking of the most commonly diagnosed cancer in women in 2023 [43]. American women have a 1 in 33 lifetime chance of developing uterine cancer [43]. Historically, endometrial hyperplasia has been classified as simple or complex, with or without atypia, with a risk of malignant progression ranging from 1 to 43% [44]. The term endometrial intraepithelial neoplasia (EIN) is now well established (previously termed atypical endometrial hyperplasia) and is considered a precursor to endometrioid endometrial cancer. All other types of endometrial hyperplasia are benign and can be managed medically [44]. Most endometrioid carcinomas differentiate well to moderately and occur in the background of endometrial hyperplasia. These tumors, also known as type 1 (low-grade) endometrial cancer, have a good prognosis. They are related to sustained unopposed estrogenic stimulation, thus are estrogen-dependent or estrogen driven. Only about 10% of endometrial cancers are type 2 (high-grade) lesions. Women with such carcinomas are at high risk of recurrence and metastatic disease [45]. Endometrial cancer has many risk factors, including increasing

Table 2 Relationship between EDC exposure and reproductive tissues in in vivo animal studies

EDC	Concentrations	Results	Reproductive Disorder	Epigenetic modulation	References
BPA	0.1, 1, 10, 100, or 1,000 μg/kg/day	Significant Wolffian remnants and uterine squamous metaplasia and vaginal adenopathy are present in BPA-treated CD-1 mice.	Squamous metaplasia of the uterus and adenopathy of the vagina	Uninvestigated	[46]
BPA	5 mg/kg	*Hoxa10* mRNA and protein expression were increased by 25%; cytosine-guanine dinucleotide methylation was decreased from 67 to 14% in the promoter and from 71 to 3% in the intron of Hoxa10.	Implantation failure, infertility	DNA methylation	[21]
BPA	100,1000 μg/kg/day	Endometriosis-like structures were found in the adipose tissue surrounding the reproductive tract of BPA-treated BALB-C mice, with both glands and interstitium, and they expressed estrogen receptors and *HOXA-10*. In addition, the incidence of adenomatous hyperplasia with cystic endometrial hyperplasia and dysplasia was significantly higher in the treated group.	Endometriosis	Uninvestigated	[77]
BPA and DES	50 mg/kg/day for BPA; 1 mg/kg/day for DES	Genistein inhibited *EZH2* and reduced levels of *H3K27me3* inhibitory markers in chromatin thus increased risk of uterine tumorigenesis	Uterine fibroids	Histone modification	[56]
BPA	5.0 mg/kg/day	The expression of *Tgfβ*, *Scd1*, *Ret* was significantly up-regulated; *Fbln2*, *Muc1*, and *Lcn2* down-regulated; ERα binding genes had lower levels of methylation than did all other genes.	Endometrial hypo-/hyperplasia, uterine cancer, breast cancer, ovarian cancer, and infertility	DNA methylation	[100]
DES	2 μg/μl	Treatment of Syrian hamsters with DES on the day of birth resulted in a 100% incidence of uterine hyperplasia/dysplasia in adulthood; the majority of which developed into neoplasia (endometrial adenocarcinoma). The progression of neonatal DES-induced dysplasia/tumor phenomena also included a cascade of altered microRNA expressions. miR-21, 200a, 200b, 200c, 29a, 29b, 429, 141 were up-regulated while miR-181a was down-regulated in the initial stage, and miR-133a was down-regulated in the boosting phase.	Endometrial adenocarcinoma	mi-RNA alterations	[47]
NP	500 μg/kg/day	Serum E2 levels in exposure group were lower and endometrial hyperplasia was observed in the exposure group; CPTI, AMPK, TSC1, TSC2, PPAR-γ and mTOR were obviously downregulated in the exposure group, while p-mTOR expressed dramatically higher in the exposure group.	Endometrial hyperplasia	Uninvestigated	[49]
BPA	100, 1,000, or 10,000 μg/kg/day	Exposure to BPA as low as 100 μg/kg/day impaired embryonic implantation in mice; BPA can affect decidualization of the uterus in mouse models.	Infertility	Uninvestigated	[93]
BPA	60 μg/kg/day	Chronic BPA treatment is utero-trophic. BPA could promote epithelial proliferation, decrease the expression of PR target HAND2, upregulated FGF signaling (*Fgf9*, *Fgf18*); induce differential methylation at the *Hand2* promoter and increase expression of methylation related factors (KLFs, STATs, HIFs).	Endometrial hyperplasia	DNA methylation	[12]
BPA, BPE, BPS	0.5–50 μg/kg/day	Accelerated the onset of puberty, exhibited abnormal estrous cyclicity and mating difficulties, reduced pregnancy rates, parturition, and nursing issues in F3 females.	Infertility	Uninvestigated	[112]
Phthalate mixtures (35% DEP, 21% DEHP, 15% DBP, 8% DiBP, 15% DiNP, 5% BzBP)	20 μg/kg/day, 200 μg/kg/day, 200 mg/kg/day, and 500 mg/kg/day	Decreased expression of Hand2 in the subepithelial matrix of F2 CD-1 mice; a higher incidence of multilayer luminal epithelium and dilation of large endometrial glands were observed in the exposure group of all generations.	Endometrial hyperplasia	Uninvestigated	[50]

Table 2 (continued)

EDC	Concentrations	Results	Reproductive Disorder	Epigenetic modulation	References
PCB126	10nM	15 *m6A*-tagged transcripts are differentially methylated due to PCB126 exposure, affecting developmental gene expression patterns.	Uninvestigated	m6A modifications	[113]

age, long-term exposure to unopposed estrogen, obesity, diabetes, menstrual periods for decades, never having children, a history of breast cancer, prolonged use of tamoxifen, and first-degree family members with endometrial cancer [45]. Although the experimental evidence available is quite limited, it is reasonable to believe that EDCs have the potential to promote the progression of endometrial cancer since a considerable number of EDCs resemble estrogen (Fig. 1).

No epidemiological data were retrieved for EDCs and endometrial hyperplasia. Significant Wolffian remnants and uterine squamous metaplasia and vaginal lymphadenopathy have been reported in BPA-treated CD-1 mice [46]. Squamous metaplasia is often associated with complex atypical hyperplasia and endometrioid carcinoma. Treatment of Syrian hamsters with DES has also been shown to result in a 100% incidence of uterine hyperplasia in adulthood, with a significant proportion of them progressing to endometrial adenocarcinoma [47].

An in vivo study also demonstrated that when young mice exposed to DES became adults, they developed estrus cycle disorders, uterine weight loss, significant hyperplasia of the myometrium and endometrium [48]. Chronic low-dose nonylphenol exposure (500 μg/kg·bw/d for 8 weeks) was associated with altered serum 17β-estradiol (E2) levels and endometrial hyperplasia in female rats (Table 2) [49]. It has also been shown that prenatal exposure to environmentally relevant phthalate mixtures can lead to changes in uterine morphology and function in mice in a multigenerational manner. Pregnant CD-1 female rats were given an oral phthalate mixture (20 μg/kg/day, 200 μg/kg/day, 200 mg/kg/day, and 500 mg/kg/day) from 10.5 gestation days to labor. The results showed that exposure to phthalate mixtures resulted in decreased progesterone levels in the F2 treatment group. In the exposure group of phthalate mixtures of all generations, a higher incidence of multilayer luminal epithelium and large endometrial gland dilation was observed (Table 2) [50].

Only one in vitro study on environmental endocrine disruptor and endometrial hyperplasia was found. It showed that BPA could increase the growth rate and colony formation efficiency of endometrial cancer cell lines (RL95-2) in a dose-dependent manner, induce epithelial-mesenchymal transition (EMT) and the expression of cyclooxygenase-2 (COX-2) genes, and promote the migration and invasion of RL95-2 cells [51].

EDCs and leiomyomas (uterine fibroids)

Uterine fibroids are benign monoclonal neoplasms of the myometrium, which are the most common tumors in women worldwide, causing problems for more than 70% of women worldwide. In addition to containing a large amount of fibrous extracellular matrix, fibroids also contain smooth muscle and fibroblast components, both of which contribute to the pathogenesis process. The pathophysiology and clinical symptoms of fibroids are extremely heterogeneous. They are also part of a family of diseases, some of which have malignant behavior but are generally benign, namely endometriosis and adenomyosis. Several risk factors, such as age, ethnicity, obesity, parity, hypertension, vitamin D deficiency, and diet later in life, contribute to the pathogenesis of uterine fibroids. Early exposure to EDCs reprograms fibroid stem cells and increases the risk of fibroids. The risk of fibroids is also related to race, black women have a higher risk of developing uterine fibroids early in life and are more severely ill than white women [22]. Clinically, uterine fibroids account for one-third to one-half of all hysterectomies and are associated with significant morbidity and medical costs in women of childbearing age [52]. Current treatments are mainly surgical and interventional treatments. However, we expect the emergence and spread of non-invasive therapies. At present, several important pathways and mechanisms are being studied, such as sex hormones, extracellular matrix (ECM), Wnt/β-catenin, TGF-β, growth factors, epigenetic, and epi-transcriptomic modulation, YAP/TAZ, Rho/ROCK, and DNA damage repair pathways, which contribute to the development of uterine fibroids [22, 52]. These studies contribute to further understanding of the clinical heterogeneity of the disease and lead to individualized treatment.

Environmental exposure during sensitive developmental windows can reprogram normal physiological responses and alter disease susceptibility later in life, a process known as developmental reprogramming (Fig. 2).

The risk of uterine fibroids in women exposed to DES prenatally was related to race. An epidemiological study showed that 5 black women who had been exposed to DES prenatally all had uterine fibroids, while the rate among white women was 76% [53]. An extensive prospective study also indicated that women prenatally exposed to DES have a higher incidence of fibroids compared to non-exposed ones, especially in the first trimester [54]. In addition, exposure to OPEs, APs, and phthalates was

Table 3 Relationship between EDC exposure and reproductive tissues in in vitro studies

EDCs	Concentrations	Cell type studied	Results	Reproductive disorder	Epigenetic modulation	References
DES, and E2-BSA	E2-BSA (50 nM and 100 nM), DES (100 nM)	uterine myometrial cells, MCF-7 cells	During windows of uterine development that are vulnerable to developmental reprogramming, activation of this ER signaling pathway by DES led to phosphorylation of EZH2 and decreased levels of trimethylation of lysine 27 on histone H3 in chromatin of the developing uterus.	Uterine fibroids	Histone modification	[17]
BPA	10nM	human endometrial carcinoma cell line (RL95-2)	BPA increased growth rate and colony-forming efficiency in a dose-dependent manner, induced EMT and *COX-2* gene expression, and facilitated the migration and invasion of RL95-2 cells.	Endometrial cancer	Uninvestigated	[51]
DEHP	10, 100, and 1000 pmol	Human endometrial stromal cell (ESC) from premenopausal women who underwent hysterectomy for carcinoma in situ	DEHP exposure increased p-ERK/p-p38 and NF-κB mediated transcription. DEHP induced ER-α expression in a dose-dependent manner.	Endometriosis	Uninvestigated	[114]
DEHP	0.2, 2, 20 and 200μM	primary cultured endometrial cells, *Ishikawa*	DEHP at human-relevant concentrations could induce an inflammatory response in primary cultured endometrial cells, and PPARγ served as a mediating receptor in the inflammatory response.	Endometriosis	Uninvestigated	[115]
BPA	10, 10^3 and 10^5 nM	human endometrial stromal cells	BPA was demonstrated to diminish miR-149 expression through the *ARF6-TP53-CCNE2* pathway to disturb cell cycle arrest and trigger migration and invasion for cancer metastasis. BPA also increased miR-107 expression to impair hedgehog signaling *SUFU-GLI3* pathway and disrupted the DNA repair function for cancer cell proliferation.	Endometrial cancer	miRNA alterations	[101]
BPA	1ng/ml, 10ng/ml, 0.5 μg/ml, 10 μg/ml, 20 μg/ml	human uterine stromal fibroblasts	BPA impaired in vitro decidualization of uterine stromal fibroblasts by decreasing steroid hormone receptor expression (progesterone receptor and estrogen receptor-α) at 20 μg/ml.	Infertility	Uninvestigated	[116]
BPA	0.01, 0.1, or 1 μg/mL	Ishikawa cells	BPA down-regulated SGK1 and ENaCα protein expression through estrogen receptors in Ishikawa cells.	Infertility	Uninvestigated	[93]
BPA	30nM, 300nM or 3μM	human endometrial stromal cells (HESCs)	BPA downregulated miR-27b and targeted *VEGFB* and *VEGFC*, which are critical to vascularization and angiogenesis of the endometrium in the menstrual cycle and decidualization.	Endometriosis, implantation failure	miR-27b alteration	[14]
BPA	1,10,100μM	Ishikawa, Choriocarcinoma Jeg-3 (ATCC HTB-36) cells	BPA of 10 and 100 μM inhibited the adhesion of Jeg-3 spheroids to Ishikawa cells. BPA treated DSCs inhibited Jeg-3 spheroid outgrowth and invasion upon coincubation. BPA inhibited the invasion ability of Jeg-3 spheroids via the ERs pathway, downregulation of *MMP2/MMP9* and upregulation of *TIMP1/*. Endothelial receptivity ability was also impaired by BPA treatment since receptivity markers of *LIF*, *EGF*, *MUC1* and *integrin aVβ3* were downregulated.	Infertility, pregnancy loss	Uninvestigated	[117]
PFAS	1μM	human endometrial cells	PFOA co-culture gave rise to significant dysregulation of the gene cascade of embryo implantation and endometrial receptivity. The most significant dysregulated genes were *ITGB8*, *KLF5*, *WNT11*, *SULT1E1*, *ALPPL2*, and *G0S2*.	Infertility	Uninvestigated	[92]

Table 3 (continued)

EDCs	Concentrations	Cell type studied	Results	Reproductive disorder	Epigenetic modulation	References
BPA	10 pM, 100 pM, 1 nM, 10 nM, 100nM, 1 μM, 10 μM	endometrial stromal cells	BPA exposure induced morphological change of decidualized endometrial stromal cells, with down-regulating expression of *MLL1*, HOXA*10*, *PRL* and *IGFBP-1*, induction of *EZH2* during in vitro decidualization. Furthermore, the decreased H3K4me3 and the increased H3K27me3 at *HOXA10*, *PRL* and *IGFBP-1* promoter regions were consistent with the expression of *MLL1* and *EZH2* respectively.	Pregnancy loss	Histone modification	[9]
BPA	1 nM, 10 nM, 100 nM	human endometrial stromal cells (HESCs)	BPA strengthened HESCs Invasion by increasing MMP2 and MMP9 expressions via GPER-mediated MAPK/ERK signaling pathway.	Endometriosis	Uninvestigated	[80]
BPA	1 nM, 10 nM, 100 nM	primary endometrial epithelial cells (pEECs) and primary endometrial stromal cells (pESCs)	BPA caused the imbalance of ERβ and ERα in eutopic endometrium, stimulated the proliferation character of ERβ via a GPER/PI3K/mTOR-mediated and WDR5/TET2-dependent epigenetic pathway, led to the hypomethylation in CpG islands and the upregulation of H3K4me3 levels in the ERβ promoter and Exon 1.	Endometriosis	DNA methylation and histone modification	[8]
Phthalates	0.1, 1, and 10 μM	primary endometrial stromal cells (EnSC), primary endometrial epithelial cells (EnEC), and Ishikawa	There was no significant effect on viability after 72 h of exposure to DEHP. None of the investigated markers of endometriosis were altered after acute DEHP exposure, nor was the expression of steroid receptors. After exposure to DEHP 10 μM, the invasiveness of EnSC enhanced significantly.	Endometriosis	Uninvestigated	[81]
HCB, p,p'-DDE, PCB180, PCB170, PFOS, PFOA, BPA, BPF, MEHP	1 μM	primary endometrial stromal cells	HCB, p,p'-DDE and PFOS significantly reduced decidualization. BPA decreases prolactin secretion but does not significantly affect kinase activity. None of the EDCs was cytotoxic, according to the evaluation of total protein content or activity of the viability marker casein kinase 2 in lysates.	Infertility	Uninvestigated	[94]

demonstrated to be associated with an elevated risk of uterine fibroids in premenopausal women [55]. However, these data are slightly controversial due to limited sample size and short half-lives of the investigated EDCs.

An in vivo study on Eker rats demonstrated that only genistein inhibited *EZH2* and reduced levels of *H3K27me3* inhibitory markers in chromatin thus increasing the risk of uterine tumorigenesis [56].

Interestingly, an earlier in vitro study revealed that DES can induce the regulation of EZH2 and changes in histone methylation levels through the signaling pathway of estrogen receptors connected to PI3K/AKT, and the subsequent effect was lowering the methylation level of inhibitory histone H3K27, leading to a similar conclusion, exposure to DES during the window-sensitive period may reprogram the expression profile of genes previously identified as targets of xenoestrogen induced developmental reprogramming in uterine myometrial cells [17].

EDCs and endometriosis

Endometriosis, a disease in which endometrium-like tissue grows outside the uterine cavity, affects approximately 10% (190 million) of women of reproductive age and girls worldwide [57]. The disease is a chronic condition that is accompanied by severe, life-damaging dysmenorrhea, dyspareunia, defecation and/or dysuria, chronic pelvic pain, bloating, nausea, fatigue, and sometimes depression, anxiety, and infertility [58]. Given these effects, endometriosis should be considered a public health problem rather than an individual disease. The cause of endometriosis is unclear. Previous hypotheses include menstrual reflux and cell metaplasia [59]. Currently it is proposed that inflammatory factors, immune disorders, hormones, genetic and epigenetic factors, and environmental factors may work synergistically to cause endometriosis [59–62]. Some recent studies have shown the potential role of the gut microbiota [63]. In addition, endometriosis is known to be estrogen-dependent; estrogen increases the inflammation, growth, and pain

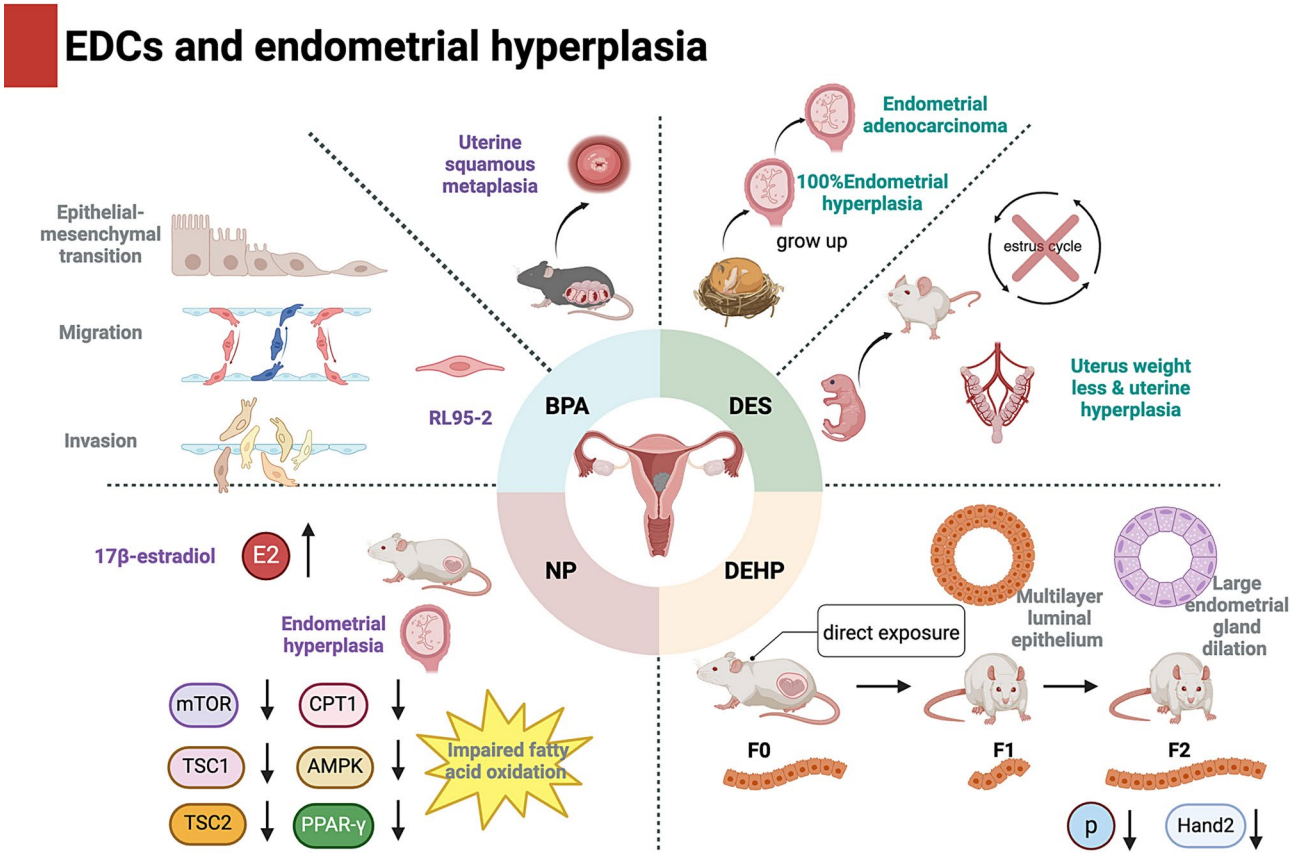

Fig. 1 Four EDCs have been shown to have links with endometrial hyperplasia [46–51]. BPA can induce epithelial-mesenchymal transition (EMT) and promote the migration and invasion of RL95-2 cells. BPA-treated CD-1 mice were reported to develop uterine squamous metaplasia. Treatment of Syrian hamsters with DES has also been shown to result in a 100% incidence of uterine hyperplasia in adulthood, with a significant proportion of them progressing to endometrial adenocarcinoma. When young mice that have been exposed to DES became adults, they developed estrus cycle disorders, uterine weight loss, significant hyperplasia. Nonylphenol exposure was associated with altered serum 17β-estradiol (E2) levels and endometrial hyperplasia in female rats. CPTI, AMPK, TSC1, TSC2, PPAR-γ and mTOR were down-regulated in utero in the exposure group, suggesting impaired fatty acid oxidation. Pregnant CD-1 female rats were given an oral phthalate mixture (F0). Decreased and increased luminal epithelial cell proliferation in F1 and F2 generations could be detected respectively. Reduced progesterone levels and Hand2 expression in the subepithelial matrix in the F2 treatment group were also demonstrated. For all generations, a higher incidence of multilayer luminal epithelium and large endometrial gland dilation was observed. Figure drawn by the author using BioRender based on information in the literature

associated with the disease. There is currently no cure, but symptoms can be treated with medical treatment (NSAIDs and analgesics, hormonal drugs such as GnRH analogs) or, in some cases, surgery. For patients who do not respond to hormone therapy, emerging drugs (particularly GnRH antagonists, selective estrogen or progesterone receptor modulators, antiangiogenic drugs, antioxidants, immunomodulators, and epigenetic agents) are promising new therapies, although they require more thorough evaluation [64].

EDCs such as diethylstilbestrol (DES), dioxins, BPA and phthalates have been linked to the development of endometriosis by altering the expression of genes involved in the immune system and inflammation [59]. A systematic review suggests that exposure to non-persistent endocrine disruptors, particularly bisphenol A and phthalates, may affect endometriosis. For instance, several studies found that higher urinary concentrations of BPA were linked to an increased risk of endometriosis. However, some studies did not observe a significant association, possibly due to differences in study design, population characteristics, or confounding factors. The association between phthalate exposure and endometriosis is more complex. While some studies found a significant association between certain phthalate metabolites (e.g., MEHP, MEHHP, MEOHP, MECPP) and endometriosis, others did not. The inconsistency may be attributed to variations in the specific phthalate metabolites examined, differences in study populations, and the use of different biomarkers and statistical models [65] (Fig. 3).

Other EDCs were also found to affect endometriosis, including parabens, benzophenones and non-persistent pesticides. Only one study has investigated the relationship between paraben exposure and endometriosis,

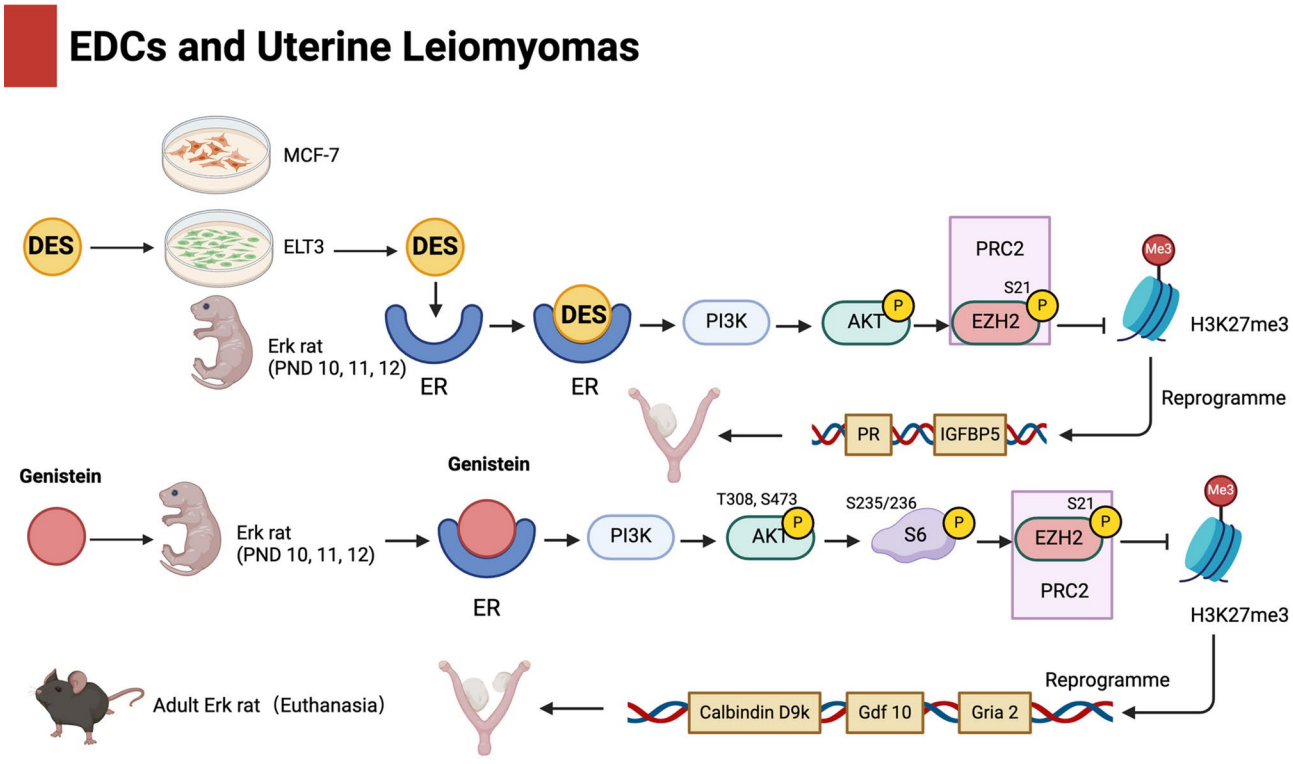

Fig. 2 Estrogenoids contribute to the development of uterine fibroids through alterations in epigenetic pathways [17, 56]. DES exposure activated the PI3K/AKT pathway in cells of MCF-7 and ELT3, in neonatal Eker rats during postnatal days 10, 11, 12, phosphorylating EZH2 at S21 and reducing H3K27Me3, leading to gene reprogramming of PR and IGFBP5, increasing the risk of uterine leiomyoma. Genistein exposure in neonatal Eker rats during postnatal days 10, 11, 12, activated PI3K/AKT signaling, phosphorylating AKT at S473/T308 and S6 at S235/236. This leads to EZH2 phosphorylation at S21, reducing H3K27me3 levels and increasing estrogen-responsive gene expression, promoting uterine leiomyomas. Figure drawn by the author using BioRender based on information in the literature

finding a significant association between methylparaben (MeP) concentration and the occurrence of endometriosis. However, this finding is preliminary and requires further validation through additional research [66]. Two studies have explored the link between benzophenone exposure and endometriosis, with conflicting results. One study reported a significant association between certain benzophenones (BP-1 and BP-3) and endometriosis, while another study did not find a significant relationship. The inconclusive nature of these findings highlights the need for more extensive research in this area [67].

A single study examined the effect of non-persistent pesticides (organophosphate and synthetic pyrethroids) on endometriosis risk, observing a significant association between endometriosis and the urinary concentration of diazinon, chlorpyrifos, and chlorpyrifos-methyl. This suggests that exposure to certain non-persistent pesticides may also play a role in endometriosis development [65].

A population-based case-control study of endometriosis which included 143 surgically confirmed cases of endometriosis and 287 population-based controls quantitatively measured total urinary BPA concentrations and suggested that higher total urine BPA concentrations were associated with non-ovarian pelvic endometriosis, but not with ovarian endometriosis [68]. In addition, a case-control study in Korea found that plasma concentrations of monoethylhexyl phthalate and di(2-ethylhexyl) phthalate were significantly higher in patients with advanced-staged endometriosis. In addition, the increase in plasma levels of monoethylhexyl phthalate, the main metabolite of DEHP, was more pronounced than that of DEHP in patients with advanced-stage endometriosis [69]. Fernandez et al. conducted a case-control study to assess the relationship between endometriosis and phthalate and BPA exposure by biomarker analysis in urine. This study assessed the relationship between endometriosis and metabolites in all subgroups but was not statistically significant. Although no evidence of a causal relationship was found, this study helps indicate that additional analyzes must be performed to assess the association between endometriosis and suspected EDC compounds [70].

The strongest association of a link between endometriosis and EDCs is for the dioxin-like substances that make up polychlorinated dioxins (PCDD/F) and biphenyls (PCBs) which are halogenated aromatic hydrocarbons with stable chemical properties and fat solubility. Based

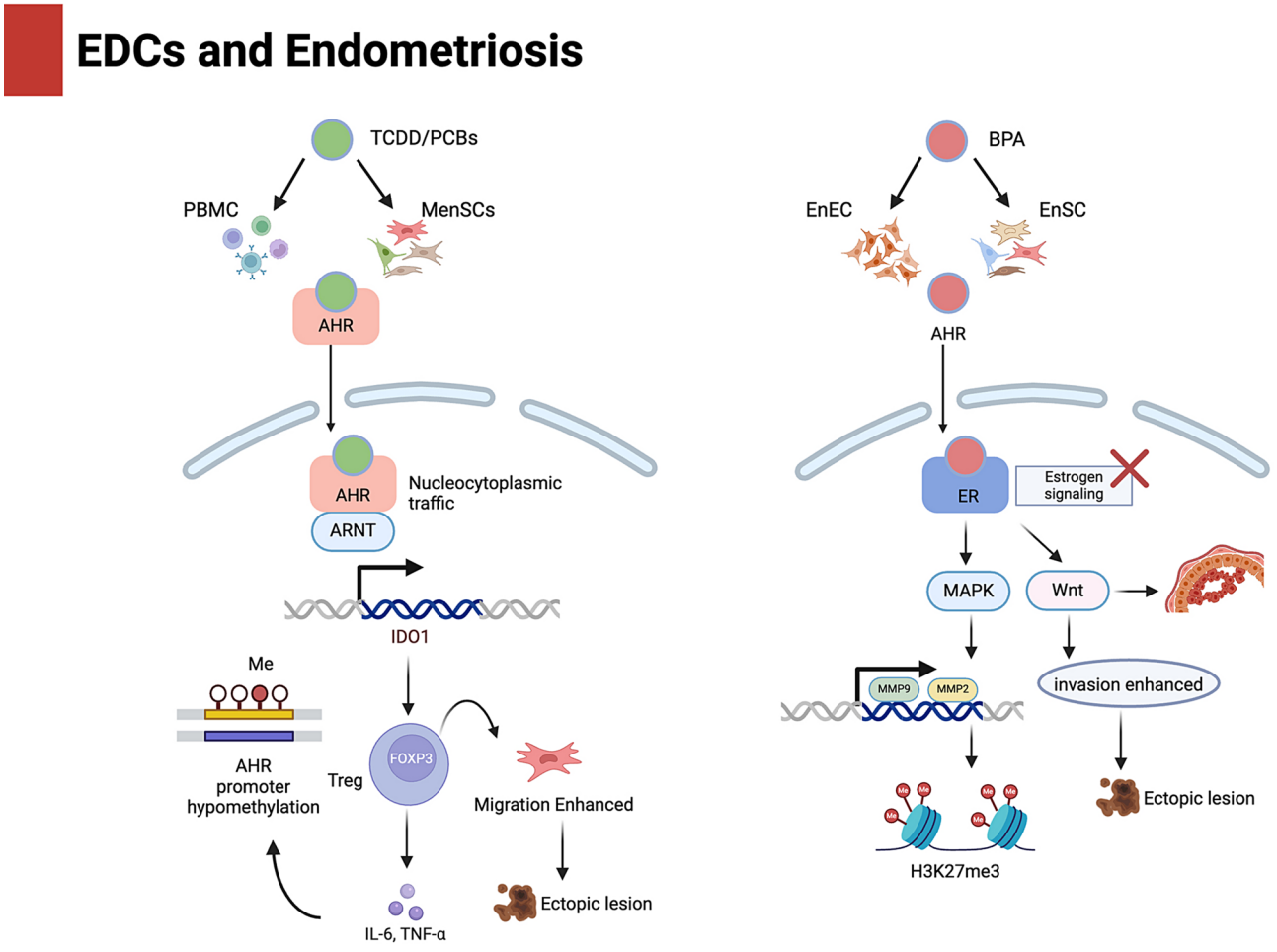

Fig. 3 Several classical mechanisms of EDCs that contribute to the development of endometriosis [79, 80]. Under normal conditions, AHR is located in the cytoplasm, bound to a complex of proteins. In TCDD or PCBs treated PBMC and MenSCs, they both bind to AHR, forming a complex with ARNT. This complex is then transported into the nucleus. Once in the nucleus, the AHR/ARNT complex promotes the transcription of IDO1, upregulating FOXP3 expression, increasing the secretion of IL-6 and TNF-α, which promotes AHR promoter hypomethylation, and also enhanced MenSCs migration, ultimately promoting the formation of ectopic lesions. BPA acts on primary endometrial stromal cells (EnSC) and primary endometrial epithelial cells (EnEC) by binding to its receptor GPER. This interaction blocked estrogen signaling and triggered the MAPK/ERK signaling pathway, leading to upregulated expression of MMP2 and MMP9, which increased the H3K27me3 level. BPA also activated the Wnt signaling pathway, further promoting cell proliferation and invasion, which contributed to the formation of ectopic lesions. Figure drawn by the author using BioRender based on information in the literature

on epidemiological data from various populations, PCBs have been linked to the development of endometriosis to the extent that it has been confirmed to be associated with endometriosis, and it can be concluded that PCB exposure increases the risk of endometriosis [71–75].

Animal studies have further clarified the link between EDCs and endometriosis. Oral administration of high levels of ethinyl estradiol (EE) to mice on days 11 to 17 of gestation resulted in an increased incidence of endometriosis lesions in the next generation [76]. DES has very strong and long lasting EE-like activity. Koike et al. demonstrated that in mice exposed to DES, sustained expression of lactoferrin and EGF genes can be observed in utero [76]. This study suggested that DES can cause long-lasting changes in gene expression, which could persist throughout development and potentially continue into adulthood. Since lactoferrin and EGF genes play roles in various biological processes, including cell proliferation, differentiation, and immune responses, the altered gene expression caused by DES could disrupt normal developmental processes, potentially leading to dysfunction in the reproductive system. It provides insights into the potential developmental impacts of DES and highlights the necessity for further investigation into the long-term effects of EDCs on reproductive health and development.

In addition, animal studies have demonstrated that prenatal exposure of mice to BPA could induce atypical hyperplasia, endometrial polyps [46], and endometriosis [77]. In rodent studies, BPA exposure could impair uterine receptivity and alter uterine morphology [20, 21, 78].

In vitro studies have been used to try and determine the mechanism by which EDCs promote endometriosis.

These studies are outlined in detail in Table 3. Tanha et al. found that TCDD may promote endometriosis progression through mechanisms such as AHR activation, Tregs induction, IDO1 activation and inflammatory cytokine regulation. TCDD treatment increased AHR, FOXP3, IDO1, IL-6, and Treg levels in the endometriosis group while decreased AHR and IDO1 levels in endometriosis PBMCs [79].

Upregulation of matrix metalloproteinase (MMP) 2 and MMP9 is involved in the development of endometriosis. In vitro studies have shown that BPA exposure can increase the expression of certain genes involved in endometriosis, such as matrix metalloproteinases (MMP) 2 and MMP9, in a dose-dependent manner [80].

Interestingly, an in vitro study exploring whether DEHP in primary endometrial stromal cells (EnSC), primary endometrial epithelial cells (EnEC), and the human endometrial adenocarcinoma cell line Ishikawa correctly mimics the changes described in the endometrium in women with endometriosis found no significant changes in endometriosis markers or steroid receptor expression after acute DEHP exposure [81].

While epidemiological and animal study evidence suggests an association between different EDCs and endometriosis, many further in vitro and animal studies are required to fully understand the mechanisms underlying this association with disease progression.

EDCs and infertility

Female fertility is very sensitive to hormone imbalance. Hence one of the most common reproductive disorders associated with EDCs is infertility. According to the World Health Organization and the American Society of Reproductive Medicine [82], infertility is a reproductive disease defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse. In April 2023, WHO launched the Global Infertility Prevalence Estimates. These estimates show that approximately 1 in 6 people around the world struggle with infertility with little variation among high, middle, and low-income countries [83]. Until 2020, the global prevalence of infertility was about 50–70 million couples [82]. In the female reproductive system, infertility may be caused by a variety of abnormalities of the ovaries, uterus, fallopian tubes, and endocrine system, among others. Uterine disorders could be inflammatory (such as endometriosis), congenital (such as septate uterus), or benign (such as fibroids). In addition to these, increasing age, abnormal weight (over or under), sexually transmitted diseases, tobacco, and certain medical treatments (such as oncology therapy) are all risk factors for infertility [84]. Infertility can be primary or secondary; primary infertility is when a person has never achieved pregnancy, and secondary infertility refers to at least one previous pregnancy [85]. Secondary infertility is the most common form of female infertility worldwide, usually due to genital tract infections.

There exists moderate evidence for a negative association between BPA, PCBs, organochloride pesticides, and female fertility [26, 86]. A cross-sectional study suggested EP and mixtures of benzophenones, TCS, and BPA were related to infertility among U.S. reproductive-age women [87]. In women, prenatal exposure to diethylstilbestrol (DES) is associated with genital tract abnormalities, menstrual irregularities, infertility, and pregnancy complications [88]. Titus et al. (2006) found that there may be an increase in infertility in daughters born to women exposed to DES in utero but this observation was not confirmed in later studies [89–91]. In a follow-up population study in 2018, 11.6% of exposed and 9.3% of unexposed women sought medical help for infertility [91]. Third-generation women did not appear to encounter more fertility issues than controls [91]. In contrast, a retrospective observational study in France which assessed reproductive tract defects, fertility, and pregnancy outcomes in daughters of women and men exposed to DES prenatally found no association between reproductive dysfunction and prenatal exposure to DES [88]. Their data did suggest that there was a high incidence of uterine defects, particularly aplastic uteruses [88]. Inconsistent results on third-generation pregnancy outcomes warrant further investigation. These results must be considered preliminary due to the small number of patients (759 daughters), limited follow-up time after birth due to the young age of the study population, and observational methods [88].

Di Nisio et al. conducted a cohort study plus in vitro cell experiments to study the interference of PFAS with endometrial hormone regulation. The cohort study consisted of 146 exposed women aged 18–21 years and 1080 unexposed controls from the Veneto region of Italy, one of the four regions globally contaminated with PFAS, showed that the exposed group had significantly higher age at menarche and frequency of menstrual irregularities [92].

The majority of studies investigating the association between EDCs and infertility are focused on impacts on the ovary and not the uterus. Therefore, there are few animal studies specifically studying how EDCs may impact uterine function in terms of fertility. However, the association between BPA and embryo implantation failure has been investigated in a combination of animal and cell models, and it was shown that exposure to BPA as low as 100 mg/kg/day impaired embryo implantation in mice [93]. Many further studies are required to delineate the impact of EDCs on uterine function vs. ovarian function in terms of reproductive health.

While animal studies are lacking several in vitro studies have been performed. BPA affected the decidualization of the uterus in mouse models and can also downregulate the expression of SGK1 and ENaCa proteins through estrogen receptors in Ishikawa cells [93]. Lavogina et al. investigated the effects of nine selected EDCs on decidualization of primary human endometrial stromal cells. Results showed that the decidualization-inducing mixture upregulated protein kinase activity and prolactin secretion in all female cells. p, p'-DDE, HCB, and PFOS significantly reduced decidualization, and bisphenol A (BPA) reduced prolactin secretion but did not significantly affect kinase activity. These results suggest that the ubiquitous presence of EDCs in the blood circulation of women of childbearing age can reduce decidualization of human endometrial stromal cells in vitro. Altered decidualization patterns in women may impact readiness for embryo implantation as well as menstruation. Future studies need to focus on detailed hazard assessments to determine the possible risk of female EDC exposure to endometrial dysfunction and implantation failure (Table 3) [94].

Experiments on Ishikawa cells, on the other hand, reported significant dysregulation of the genetic cascade leading to embryo implantation and endometrial receptivity. This indicates the potential toxicity of PFAS to interfere with female reproductive capacity, and more research is needed to further confirm the specific mechanism (Table 3) [92].

It should be clarified that infertility due to non-uterine factors such as endometriosis and ovarian disease is beyond the scope of this section.

Epigenetic regulation

How a fertilized egg develops into an organism made up of hundreds of highly specialized cell types has always been a mystery for biologists. Epigenetics has been defined as "the study of molecules and mechanisms that can perpetuate alternative gene activity states in the context of the same DNA sequences" [95]. Epigenetic effects are reversible; the most common mechanisms are DNA methylation, histone modification, and non-coding RNA (ncRNA), which can affect transcript stability, DNA folding, nucleosome localization, chromatin compaction, and nuclear organization, with the result determining whether genes can be expressed or silenced. Nevertheless, these effects depend on the complex interplay between an individual's genetic traits and epigenetic regulation [96, 97]. Epigenetics connects genetics to the environment and disease, with harmful environmental chemicals potentially altering the epigenome rather than the DNA sequence [98]. In the study of EDCs, one of the intrinsic challenges is the difficulty in accurately measuring exposure during critical sensitive window stages or extending exposure assessment to measure the exposome over the entire lifetime. Epigenomics is a kind of omics approach that may ultimately be applied to create unique molecular 'fingerprints' that represent individual exposure, dose, biological response, and susceptibility [25].

Estrogen plays a crucial role in regulating reproductive function, and EDCs, due to their structural similarity to hormones, can mimic or block the effects of estrogen to disrupt biological processes [11, 98]. Nuclear receptors including ESR1 and ESR2, as well as other transcription factors, for instance, AR, PXR, AhR, and PPAR-γ, can be subject to regulation by EDCs [98]. Studies have shown that exposure to EDCs can alter the expression of genes involved in estrogen signaling, leading to changes in epigenetic marks such as DNA methylation and histone modifications. Here we will briefly outline the different types of epigenetic changes that may occur and then discuss the evidence for EDCs contributing to epigenetic changes that in turn may lead to different uterine pathologies.

DNA methylation

The most prominent epigenetic fingerprint is DNA methylation, which is also the major carrier of epigenetic information. DNA methylation is the addition of a methyl group to a cytosine base, usually followed by a guanosine base, resulting in cytosine-guanine dinucleotide phosphate (CpG) [25, 95]. The essence of understanding DNA methylation is to allow methylation to be replicated during DNA replication, allowing it to be preserved in the newly copied DNA. This process involves some key specific proteins that recognize CpG hemi methylated DNA. A combination contains both a "writer" (DNMT1) and a "reader" (UHRF1/NP95) of the epigenetic methyl CpG marker, and these two fractions are essential for maintaining DNA methylation [95]. DNA methylation of the AhR receptor may be a potentially useful biomarker to verify past exposure and has boosted the research of DNA methylation biomarkers responsive to EDC exposure [25].

Histone modification

Chromosomes are genetic material, carriers of genes, and their basic structural units are nucleosomes. Therefore, histones involved in nucleosome assembly are one of the important factors in determining the degree of chromatin packaging. Nucleosomes are composed of octamers formed by two copies of each of the four histone subunits H2B, H2A, H3, and H4, and DNA, about 146 bp, wound outside. Among them, amino acid residues at the N-terminus (tail) of histones are susceptible to post-translational modifications (PTMs), including acetylation, methylation, phosphorylation, ubiquitination, and other types. They alter the association between

histone and DNA structure. Some modifications loosen the interaction between histones and DNA, resulting in a loosely packed DNA conformation, known as euchromatin. In this conformation, DNA is susceptible to binding by transcription factors, leading to gene activation. On the other hand, some modifications tighten histone-DNA interactions, resulting in dense and tightly packed DNA conformations called heterochromatin. In this conformation, the DNA is not open to binding by transcription factors and results in gene silencing. Thus, modifications of histones alter chromatin structure and lead to epigenetic alterations in chromatin [7].

Non-coding RNA alteration

A non-coding RNA (ncRNA) is an RNA molecule that is not translated into a protein, one of which is closely linked to epigenetics is microRNA (miRNA). MicroRNAs are small, non-coding RNAs that are transcribed from DNA into primary microRNAs and processed into precursor and mature miRNAs that take a lead role in regulating gene expression. By base pairing, miRNAs act on complementary sequences within mRNA molecules, leading to silencing of these mRNA molecules. MiRNAs regulate protein expression after transcription [7]. It is another regulatory mechanism contributing to phenotypic variation that can occur at the post-transcriptional and transcriptional level.

EDCs and epigenetic regulation in female reproductive tissues

Epigenetics has multiple levels of regulation, relying on DNA sequences and the synergy of partially overlapping signals. The regulation of each layer increases epigenetic stability, but they are all reversible, which makes remodeling possible. Epigenetic mechanisms buffer environmental changes while allowing resilient responses to the most extreme environmental conditions. Phenotypes thus are the products of genome components, epigenetic modulation, and environmental input [95].

Many previous studies have confirmed the following points: (1) EDCs cause epigenetic modifications only during critical windows of growth and development, such as intrauterine or embryonic periods. If the exposure is in adulthood, then modification at the epigenetic level does not occur. (2) When EDCs regulate the epigenetic group of somatic cells, although it will also promote the occurrence of disease, it will not produce intergenerational effects. Only when EDCs act on germ line cells will it produce a transgenerational effect [21, 99]. Many studies have suggested that many actions of endocrine disruptors on reproductive processes are mediated by disruption or alteration of epigenetic pathways.

Endometrial hyperplasia, endometrial Cancer and infertility

Aberrant developmental programming of estrogen response genes due to EDC exposure can lead to endometrial hyperplasia, endometrial cancer and infertility (Fig. 4). Hoxa10 gene expression alterations are associated with these diseases. Hoxa10 is an essential developmental gene in embryonic uterine patterning, but it also continues to be dynamically expressed in the adult endometrium and is regulated by sex steroid hormones. It has been shown to control uterine organogenesis and is necessary for implantation [21]. In rodent experiments, Hoxa10 has been shown to be a target gene for early EDC exposure involved in mRNA and protein expression as well as promoter DNA methylation [20, 21]. BPA exposure in pregnant CD-1 mice decreased DNA methylation, leading to an increase in the binding of ER-alpha to the hoxa10 estrogen response element (ERE). A subsequent mice study demonstrated that intrauterine BPA exposure altered the global CpG methylation profile of the uterine epigenome and subsequent gene expression, preferentially affecting the expression of ER-binding genes, and that this effect on gene expression was not evident until sexual maturity [100]. This suggests that the hypomethylation caused by prenatal exposure to BPA is not an isolated case, but a common phenomenon that causes alterations in the expression of most ERα-binding genes, including HOXA10. Aberrant developmental programming of estrogen response genes can lead to uterus-related diseases such as endometrial hyperplasia, endometrial cancer, and infertility. It was further confirmed that chronic BPA exposure caused an imbalance between estrogen and progesterone [12]. On the one hand, BPA up-regulated the expression of estrogen by activating the FGF and p-ERK1/2 signaling pathways, via a mechanism associated with increased uterine expression of several methylation-related factors, including DNA methyltransferases Dnmt1 and Dnmt3b and methylated DNA binding protein Mbd2. On the other hand, it also increased the methylation of the promoter CpG island of the progesterone target HAND2, silencing the expression of HAND2, thereby down-regulating progesterone expression [12].

Exposure to estrogen-like EDCs such as diethylstilbestrol and genistein during the uterine development window has been found to activate estrogen receptor signaling pathways, leading to changes in histone modifications and the promotion of uterine tumors. Specifically, activation of PI3K or AKT pathways, rapid phosphorylation of EZH2, and decrease of H3K27me3 in the developing uterus leads to the reprogramming of estrogen-responsive genes, structural and morphological disruption of the myometrium [17, 56].

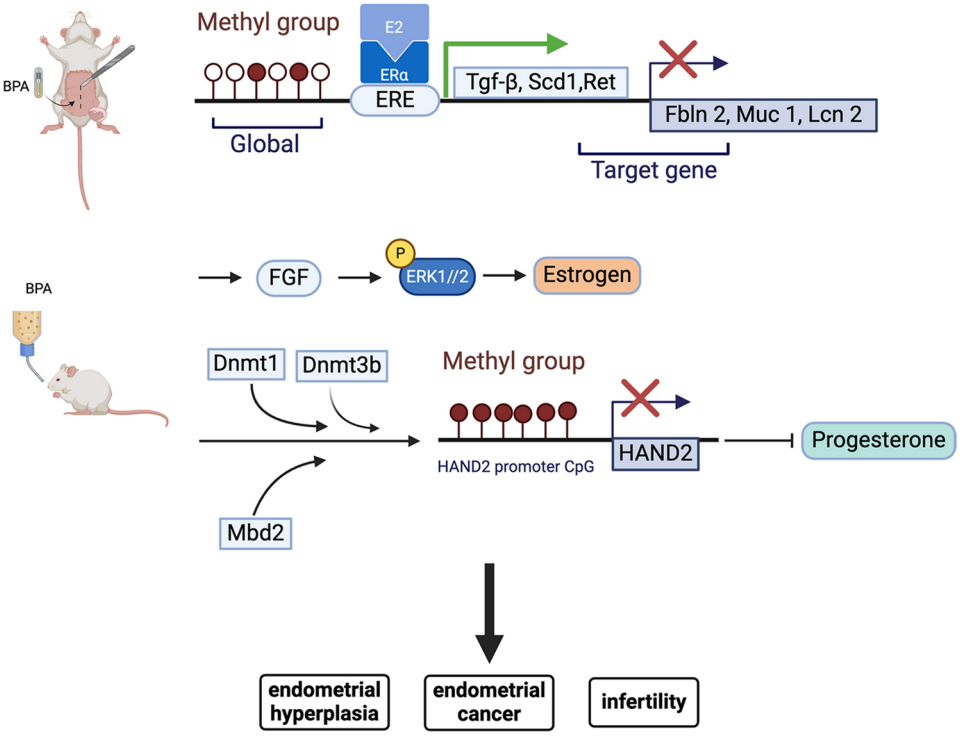

Fig. 4 How BPA contributes to the development of endometrial hyperplasia, endometrial cancer and infertility through DNA methylation alterations [12, 100]. Intrauterine BPA exposure altered the global CpG methylation profile of the uterine epigenome and subsequent gene expression, preferentially affecting the expression of ER-binding genes (upregulating Tgfβ, Scd1, Ret and downregulating Fbln2, Muc1, and Lcn2). Here, ERα binding genes had lower levels of methylation than did all other genes. BPA up-regulated the expression of estrogen by activating the FGF and p-ERK1/2 signaling pathways. On the other hand, it also increased the methylation of the promoter CpG island of the progesterone target HAND2, via a mechanism associated with increased uterine expression of several methylation-related factors, including DNA methyltransferases Dnmt1 and Dnmt3b and methylated DNA binding protein Mbd2. Hypermethylation led to the silencing expression of HAND2, thereby down-regulated progesterone expression. Figure drawn by the author using BioRender based on information in the literature

It has also been observed that BPA diminished the expression of miR-149, which disrupted the ARF6-TP53-CCNE2 pathway, triggered cell migration and invasion, interrupted cell cycle arrest, promoting endometrial cancer metastasis. Additionally, increased expression of miR-107 has been linked to the attenuation of the hedgehog signaling SUFU-GLI3 pathway and the impairment of DNA repair functions, contributing to cancer cell proliferation [101].

It was reported that progression of the neonatal DES-induced dysplasia/neoplasia phenomenon in the hamster uterus was associated with a sequence of microRNA expression alterations that differ during the initiation (up-regulated miR-21, 200a, 200b, 200c, 29a, 29b, 429, 141; down-regulated miR-181a) and promotion (down-regulated miR-133a) stages of the phenomenon [47].

Decidualization disorders

It has also been suggested that environmentally related levels of BPA exposure may impair the decidualization of endometrial stromal cells, leading to pregnancy loss (Fig. 5) [9]. Adequate decidualization of the endometrium is the gatekeeper of human embryo implantation. Embryonic factors cause only one-third of implantation failures, whereas endometrial receptivity abnormalities result in approximately two-thirds of implantation failure [102].

The study found that BPA could interrupt the balance between two histone markers (H3K4me3 and H3K27me3) by upregulating the expression of EZH2 protein and downregulating the expression of mixed-lineage leukemia 1 (MLL1) protein in endometrial stromal cells, ultimately leading to dysregulation of several key genes and impaired decidualization. This epigenetic dysregulation belonged to histone modification and was estrogen receptor-mediated, but the specific signaling pathways involved have not been studied. The decidualization marker genes involved in the in vitro study were HOXA10, PRL and IGFBP-1. The decrease of H3K4me3 and the increase of H3K27me3 in the promoter region were consistent with the expression of MLL1 and EZH2, respectively [9].

Endometriosis

Overexpression of estrogen receptor β (ERβ) in the endometrium contributes to the development of

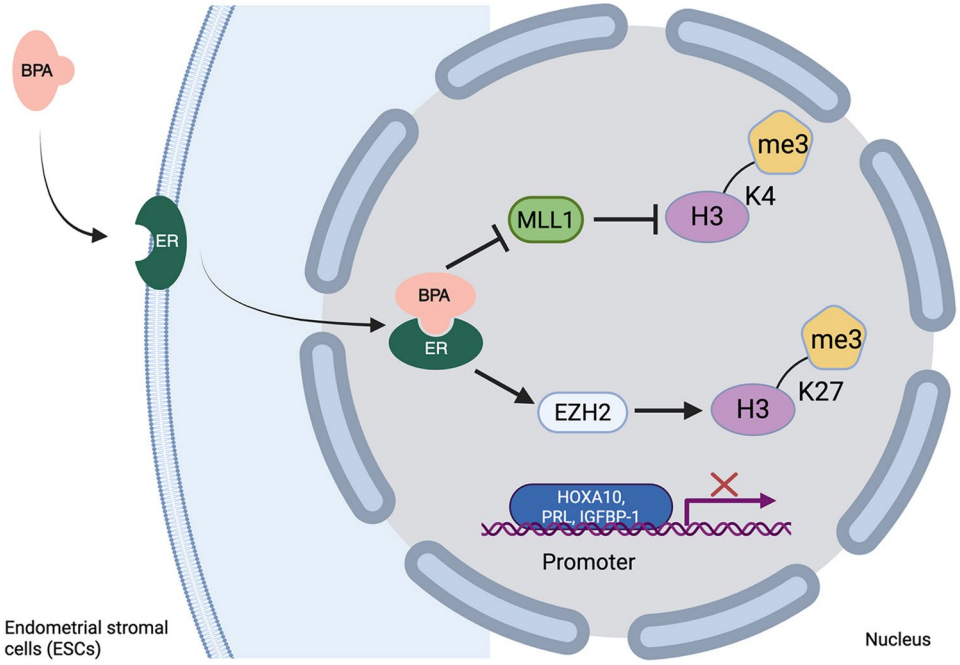

Fig. 5 How BPA impairs decidualization through histone modification [9]. BPA could bind to the estrogen receptor, interrupt the balance between two histone markers (H3K4me3 and H3K27me3) by upregulating the expression of EZH2 protein and downregulating the expression of mixed-lineage leukemia 1 (MLL1) protein in endometrial stromal cells, leading to decreasing expression of decidualization marker genes, such as HOXA10, PRL and IGFBP-1 thereby impaired the decidualization. Figure drawn by the author using BioRender based on information in the literature

endometriosis. It was demonstrated that BPA significantly upregulated H3K4me3 levels in the ERβ promoter and exon 1 by inducing WD repeat domain 5 (WDR5) expression via the G protein-coupled estrogen receptor (GPEK)-mediated PI3K/ mammalian target of rapamycin (mTOR) signaling pathway. Furthermore, BPA exposure also enhanced WDR5 and tet methylcytosine dioxygenase 2 (TET2) interactions, promoted the recruitment of WDR5/TET2 complexes to ERβ promoters and exon 1, and inhibited DNA methylation of CpG islands, thereby inducing ERβ overexpression both in epithelium and stroma, thus contributing to the development of endometriosis. This WDR5/TET2-mediated epigenetic pathway included not only DNA methylation but also histone modification [8]. On the other hand, the identification of the miR-27b target gene suggested that BPA and E2 downregulated miR-27b, resulting in upregulation of genes vital for endometrial vascularization and angiogenesis during the menstrual cycle and decidualization, which might be related to the occurrence and progression of endometriosis. Alternatively, similar changes may also result in implantation failure [14].

Bruner-Tran et al. demonstrated with in vivo and in vitro endometriosis models that the loss of progesterone sensitivity associated with exposure to TCDD in mice is biologically related to an inflammatory-like pattern of cell-cell communication in utero, possibly due to epigenetic modifications mediated by the inflammatory process. The transgenerational infertility phenotype and associated risks in these animals may be due to epigenetic silencing of PR due to ancestral TCDD exposure, associated with the hypermethylation status of the progesterone receptor gene [23].

Conclusions and future directions

There is much epidemiological, and some animal exposure studies, evidence that EDCs are associated with several uterine disorders however they receive less attention than ovarian conditions associated with EDC exposure. In addition, mechanistic studies of how different EDCs impact uterine development and function are severely lacking. One key question that is raised is that since the endometrium functionalis is shed each month with menstruation how these conditions persist in the absence of continued EDC exposure. This raised the question as to whether there was evidence for epigenetic regulation in the endometrium basalis of women with these different conditions as a result of EDC exposure. Indeed, this is a woefully understudied area of both EDC and uterine biology.

Abbreviations

AMPK	Adenosine 5′-monophosphate-activated protein kinase
Ang-2	Angiopoietin-2
ARF6	ADP-ribosylation factor 6
Ascl2	Achaete-Scute Family BHLH Transcription Factor 2
BP	Butyl paraben
BP-3	Benzophenone-3

BPA	Bisphenol A
BPAF	Bisphenol AF
BPAP	Benzofuranylpropylaminopentane
BPB	Bisphenol B
BPE	Bisphenol E
BPP	Bisphenol P
BPS	Bisphenol S
CCNE2	Cyclin E2
Cdkn1c	Cyclin Dependent Kinase Inhibitor 1 C
COX-2	Cyclooxygenase-2
CPTI	Carnitine palmitoyltransferase I
DEHP	bis(2-ethylhexyl) phthalate
DES	Diethylstilbestrol
DL-PCBs	Dioxin-like PCBs
DMRs	Differentially methylated regions
DNMT	DNA methylation transferase
DSCs	Decidualized stromal cells
E2-BSA	BSA-conjugated estradiol
EGF	Epithelial growth factor
EMT	Epithelial to mesenchymal transition
EnSC	Primary endometrial stromal cells
EP	Ethyl paraben
ER	Estrogen receptor
ERK	Extracellular signal regulated kinase
ERα	Estrogen receptor alpha
EZH2	Enhancer of Zeste homolog 2
Fbln2	Fibulin 2
FGF	Fibroblast growth factor
G0S2	G0/G1 switch gene 2
GLI3	GLI family zinc finger 3
GPER	G protein-coupled estrogen receptor
H3K4me3	Histone-3, lysine-4 trimethylation
H3K27me3	Histone-3, lysine-27 trimethylation
HAND2	Heart and neural crest derivatives expressed 2
HCB	Hexachlorobenzene
HEEC	Human endometrial endothelial cell
HIFs	Hypoxia inducible factors
HOXA10	Homeobox A10
IFN-γ	Interferon-γ
IGFBP-1	Insulin-like growth factor-binding protein 1
ITGB8	Integrin Subunit Beta 8
KLF5	Kruppel Like Factor 5
KLFs	Kruppel-like factors
Lcn2	Lipocallin 2
LIF	Leukemia inhibitory factor
m6A	The N6-Methyladenosine (m6A) modification of RNA transcripts
MAPK	Mitogen-activated protein kinase
mEHHP	mono(2-ethyl-5-hydroxyhexyl) phthalate
mEHP	mono (2-ethylhexyl) phthalate
mEP	mono-ethyl phthalate
miBP	mono-isobutyl phthalate
MLL1	Mixed-lineage leukemia 1
MMP	Metalloproteinase
MP	Methyl parabens
mTOR	Mammalian target of rapamycin
Muc1	Mucin 1
NDL-PCBs	Non-dioxin-like PCBs
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NP	Nonyl phenol
p,p'-DDE	1,1-dichloro-2,2, -bis(4-chlorophenyl)-ethene
PAI-1	Plasminogen activator inhibitor 1
PCB	Polychlorinated biphenyl
PCB126	Polychlorinated biphenyl 126
PCDD	Polychlorinated dibenzodioxins
PCDF	Polychlorinated dibenzofuran
p-ERK	Activated forms of p-MAPKs, phospho-ERK
PFAS	Perfluoroalkyl sulfonate
PFOS	Perfluorooctanesulfonic acid
PI3K	Phosphoinositide 3-kinase
p-mTOR	Phosphorylated mammalian target of rapamycin
PP	Propylparaben
p-p38	Activated forms of p-Akt, phospho-p38
PPAR-γ	Peroxisome proliferator-activated receptor gamma
PR	Progesterone receptor
PRL	Prolactin
Ret	RET proto-oncogene
Scd1	Stearoyl-CoA desaturase-1
SGK1	Serum and glucocorticoid-regulated kinase 1
Snrpn	Small nuclear ribonucleoprotein polypeptide N
STATs	Signal transducer and activator of transcription
SUFU	Suppressor of fused homolog
TCS	Triclosan
TET2	Tet methylcytosine dioxygenase 2
Tgfβ	Transforming growth factor beta induced
TIMP	Tissue inhibitor of metalloproteinase
TP53	Tumor protein p53
TSC1	Tuberous sclerosis 1
TSC2	Tuberous sclerosis 2
Ube3a	Ubiquitin-protein ligase E3A
VEGF	Vascular endothelial growth factor
VEGFB	Vascular endothelial growth factor B
VEGFC	Vascular endothelial growth factor C
VEGF-D	Vascular endothelial growth factor D
WDR5	WD repeat domain 5
WNT11	Wingless-Type MMTV Integration Site Family, Member 11
SULT1E1	Sulfotransferase family 1E, estrogen-preferring, member 1
WNT2	Wnt family member

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Data availability
No datasets were generated or analysed during the current study.

Declarations

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Not applicable.

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The authors declare no competing interests.

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