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Nonpersistent endocrine disrupting chemicals and reproductive health of women

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Nonpersistent endocrine disrupting chemicals (npEDCs) are exogenous chemicals or mixtures of industrial agents that can interfere with the normal action of hormone with a shorter half-life and lower liposolubility. These are commonly found in plastics, medical equipment, detergents, and cosmetics. Recently, role of npEDCs on the changes of ovary and/or uterus development and alterations in hormonal signaling has been emphasized. However, many controversial results exist on the effects of npEDCs and reproductive health of women. Thus, we have focused to review the scientific evidence of a causal relationship between exposure to npEDCs and representative female reproductive issues such as menstrual cycle, endometriosis, uterine fibroids, polycystic ovarian syndrome and infertility/subfertility. Though not all studies indicated a positive correlation of npEDCs with female reproductive issues, the reviewed data illustrated that the majority of the available data strengthen the evidence of reproductive health-related actions of npEDCs. In future, recommendations should be made in order to reduce human exposure to npEDCs and to protect from steadily increasing reproductive health risks.

Keywords: Endocrine disruptors; Endometriosis; Uterine fibroid; Polycystic ovarian syndrome; Infertility

Introduction

Endocrine disrupting chemicals (EDCs) are chemicals that interfere with the body's endocrine system and cause adverse developmental, reproductive, neurological, and immune effects. EDCs may mimic, in whole or in part, natural body hormones that exhibit their effects by acting on specific receptor proteins. They also bind to cell receptors, thereby blocking their interaction with natural hormones, or alter hormone metabolism. Individual EDCs may interact with more than one receptor, and multiple EDCs can interact with the same receptor, highlighting the unusual properties of environmental EDCs [1]. We can divide these chemicals according to their lipophilic nature. Chemicals with high lipophilic activity and a longer half-life are called 'persistent EDC' or 'persistent organic pollutants' (POPs), which may bioaccumulate in fat and can be biomagnified through the food chain. Representative chemicals are dioxins, dichlorodiphenyl-trichloroethylene, heptachlor, and polychlorinated biphenyls. For POPs, many epidemiologic and *in vitro* studies provided estimates of the gynecologic health risks in human populations [2-8].

There are other chemicals with a shorter half-life and lower liposolubility, which are called nonpersistent EDCs (npEDCs). Examples of npEDCs are bisphenol A (BPA), phthalates, parabens, and triclosans (TCSs). BPA (4,4'-(propane-2,2-diyl) diphenol) is a well-known EDC component of baby bottles, children's toys, dental sealants, coating of receipts, and epoxy resins used to coat the inside of food cans. Di-2-ethylhexyl phthalate (DEHP) is used as a plasticizer and is contained in a wide range of products such as plastics, cosmetics, and medical devices. Parabens (alkyl esters of 4-hydroxy benzoic

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acid) are used as preservatives in personal care products such as cosmetics and pharmaceutical products. TCS is an antimicrobial compound used in consumer products such as toothpaste, mouth wash, and hand sanitizers. In contrast to POPs, the exact effect of npEDCs on gynecologic health risk is not totally understood. These chemicals may cause subtle changes in ovary and/or uterus development and alterations in hormonal signaling, possibly resulting in variable phenotypes [9]. Although the direct effect of npEDCs on these conditions is difficult to prove, low-dose and continuous environmental exposure might play a critical role on gynecologic health. The purpose of this article was to review the scientific evidence of a causal relationship between exposure to npEDCs and representative female reproductive issues, menstrual cycle, endometriosis, uterine fibroid (UF), polycystic ovarian syndrome (PCOS), and infertility/subfertility.

Menstrual cycle

1. Bisphenol A

In rodents, the effects of BPA exposure on estrous cycle were examined in several studies [10-13]. Uterine exposure to BPA alters several apoptotic factors and causes germ cell nest breakdown, which results in estrous cycle changes [10]. BPA treatment significantly decreases serum estradiol (E2) concentration, which is accompanied by increased duration of the estrus phase, increased ovarian cell apoptosis, and decreased E2-regulated protein expression and collagen content in the uterus [11]. In contrast, high-dose BPA shortens the estrous cycle day and length [12]. Neonatal exposure to BPA leads to abnormal function of the neural network that controls the cycle. Hypothalamic LH-releasing hormone pre-mRNA processing and steroid receptor expression in nuclei controlling estrous cyclicity are permanently disrupted [13].

In humans, urinary BPA metabolites were measured in 221 healthy women and BPA was associated with shorter luteal phase. However, no association was seen in follicular phase length [14]. Analysis of the longitudinal urine samples from healthy, premenopausal women showed that BPA was associated with increased E2, which may influence the menstrual cycle [15]. Only a few associations have been reported between BPA exposure and changes in menstrual characteristics. The effects of BPA exposure on estrous cyclicity in rodents and menstrual cycle in humans are still inconclusive.

2. Phthalates

In rodents, DEHP exposure decreased the levels of estrogen and progesterone, in addition to prolonging menstrual cycles and anovulation [16]. High-dose DEHP treatments resulted in reduced serum estradiol, prolonged estrous cycles, and inhibition of ovulation [17]. Continuous exposure to DEHP during adult life prolonged the duration of estrous cycle. Low levels of DEHP disrupted phosphatidylinositol 3-kinase signaling, which resulted in abnormal estrous cycles and primordial follicle recruitment [18]. DEHP treatment showed decreased estradiol production in cultured rat ovarian tissues [19]. In cultured mouse antral follicle DEHP and mono-(2-ethylhexyl)-phthalate (MEHP) inhibited estradiol biosynthesis and inhibited mRNA expression of cyclin-D-2, cyclin-dependent-kinase-4, and aromatase (Arom) [20]. MEHP also acts on the granulosa cells by decreasing the level of cyclic adenosine monophosphate stimulated by follicle stimulating hormone and by activating peroxisome proliferator-activated receptors (PPARs), which leads to decreased Arom transcription [21]. These may suggest that phthalates alter E2 production through the decreased expression of cell cycle regulators and specific receptor-mediated responses.

In humans, high concentrations of urinary monocarboxyoctyl phthalate are associated with short luteal phase. But menstrual cycle-specific estimates of urinary phthalate metabolites were not associated with the follicular-phase length [14]. Another study did not show a consistent relationship between menstrual phase and phthalate metabolite concentrations [22]. Based on described studies, a mechanistic model explaining phthalate effects on menstrual cycle has been proposed. However, the exact effects of phthalates on menstrual cycle are inconclusive.

3. Parabens and triclosan

Parabens and paraben metabolites are associated with increased E2 levels in healthy premenopausal women. In Japanese women, butyl paraben concentrations (odds ratio [OR], 0.83; 95% confidence interval [CI], 0.70–0.99) are negatively correlated with menstrual cycle length and urinary estrogen-equivalent total paraben concentrations (OR, 0.73; 95% CI, 0.56–0.96) [23]. To date, no studies have addressed the effects of TCS on the menstrual cycle.

Endometriosis

Endometriosis has a multifactorial etiology involving genetic, hormonal, immunologic, and environmental factors [24]. As for other reproductive disorders, a direct causality between npEDCs and endometriosis is difficult to prove. Moreover, the experimental and epidemiological data are not always consistent. EDCs are of particular interest as potential contributors to endometriosis because they can alter steroidogenesis, immunologic function, and are epigenetic causal factors involved in this disease progression [25].

1. Bisphenol A

As rodents do not develop spontaneous endometriosis, experimental models are used to study the relationship between BPA and endometriosis. Oral administration of BPA increases gland nest density and periglandular collagen accumulation, characteristics of an endometriosis-like phenotype, in adult CD-1 mice. These have shown increased collagen I and III expression and decreased matrix metalloproteinase (MMP)-2 and MMP-14 expression in those tissues around the uterus [26,27]. Prenatal exposure of mouse to BPA induces an endometriosis-like phenotype in female offspring. Moreover, the effects of EDCs during critical developmental stages seem to be long-lasting [28]. In these mice, primordial and developing follicle numbers were significantly lower than those in controls [29]. These results indicate that EDCs may induce endometriotic phenotype and compromise ovarian function of the following generations.

In humans, the serum of patients with endometriosis is known to contain at least 1 of the 2 bisphenols (BPA and bisphenol B) [30]. One population-based case-control study revealed the median creatinine-corrected total urinary BPA concentrations were higher (1.32 μg/g, interquartile range [IQR], 0.79–2.21) in endometriosis patients than in controls (1.24 μg/g, IQR, 0.65–2.54). Especially for non-ovarian pelvic endometriosis, statistically significant positive associations were observed with urinary BPA concentrations [31]. In patients with ovarian endometrioma, the mean urinary concentration of BPA was found to be significantly higher than that in control subjects (5.53±3.47 ng/mL vs. 1.43±1.57 ng/mL) [32]. Some other epidemiologic studies have shown a positive association between urinary BPA levels and endometriosis [8,30,33]. In contrast, a cross-sectional study in Japanese and USA patients found no significant associations between endometriosis and urinary BPA concentrations [34,35]. Thus, not all studies have shown positive associations.

Low BPA concentrations affect human endometrial stromal cell (ESC) physiology. BPA enhanced progesterone-induced decidualization and promoted ESC migration and oxidative stress *in vitro* [36,37]. Currently, the molecular mechanisms involved in the progression of endometriosis are not well understood. Moreover, studies using parenteral routes of administration may have limited relevance, if any, to human risk assessment. Thus, the impact of BPA on reproduction is still unclear and epidemiologic data in humans are limited.

2. Phthalates

Earlier studies have analyzed the levels of phthalates in serum in relation to the risk of endometriosis. Cobellis et al. [38] were the first to demonstrate significantly higher plasma concentrations of DEHP in endometriotic women than in controls. In Korea, women with advanced endometriosis exhibited significantly higher plasma levels of MEHP and DEHP than those in control women without endometriosis [39]. Similar results were observed in Indian women [40,41].

The urinary concentration of phthalate metabolites is commonly used as a representative biomarker of exposure to DEHP because, after oral administration of DEHP, about 75% of the compound is excreted in urine in the form of DEHP metabolites after 44 hours in humans [42]. In the National Health and Nutrition Examination Survey (NHANES), a cross-sectional study of urinary phthalates revealed a significantly positive association between mono-n-butyl phthalate (MBP) and the risk of endometriosis [43]. Moreover, specific phthalates were associated with MRI-diagnosed endometriosis [34]. In the Endometriosis, Natural History, Diagnosis, and Outcomes Study, 6 phthalate metabolites [MBP, mono-[(2-carboxymethyl) hexyl] phthalate, mono (2-ethyl-5-carboxyphentyl) phthalate, MEHP, mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono (2-ethyl-5-oxohexyl) phthalate) (MEOHP) were significantly associated with increased odds of endometriosis [34].

In contrast to the above studies, a population-based case-control study conducted in the USA as part of the Women's Risk of Endometriosis study failed to demonstrate the association between specific phthalate metabolites and endometriosis risk [44], while a study in Japanese women failed to demonstrate a positive association between urinary concentrations of phthalate metabolites and the risk of endometriosis [45].

Some *in vitro* studies suggested that exposure to phthalates might play a role in the establishment of endometriosis. In particular, DEHP promotes the viability of ESCs [46], and treatment of endometrial cells with DEHP leads to significant increases in MMP-2 and MMP-9 activities, cellular invasiveness, extracellular signal-regulated kinase (ERK) phosphorylation, and p21-activated kinase 4 expression [47]. In human ESCs, DEHP exposure increases p-ERK/p-p38- and nuclear factor-κB-mediated transcription through an oxidative stress pathway. Moreover, DEHP induces the expression of estrogen receptor-α (ERα) in a dose-dependent manner [48]. Notably, in the endometrium of patients with endometriosis, DEHP induces aldo-keto reductase activity, which is involved in prostaglandin synthesis and progesterone-resistance [49]. Although *in vitro* results support the hypothesis that phthalates may be an inducer of endometriosis, further investigations will be required to definitively establish the association between phthalates and endometriosis.

3. Parabens and triclosan

ESCs exposed to TCS showed increased decidualization effect which suggested than TCS may alter the nature of normal ESCs [36]. That is the only study about TCS effects in relation to endometriosis, and no studies have addressed the possible relationship between paraben and endometriosis.

Uterine fibroid

UF is one of the most frequent gynecologic tumors among women of reproductive age and causes symptoms such as abnormal uterine bleeding, menorrhagia, and pelvic pain. It is known as an estrogen-dependent disease, and a possible involvement of EDCs has been suggested [50]. We here describe the effect of BPA and phthalate on UF. There are no studies about paraben and TCS with UF.

1. Bisphenol A

In China and the USA, the mean urine BPA concentration was significantly higher in the UF group than in controls [15,51,52]. In contrast, Korean studies revealed that the serum concentration of BPA is not related to UF progression [53,54]. Thus, epidemiological studies on BPA and UF are not consistent.

An *in vitro* study showed that BPA promoted the growth of UF cells and the expression of ERα, insulin-like growth factor-1, and vascular endothelial growth factor in a dose and time-dependent manner [55]. BPA seems to promote the proliferation of UF cells via the ERα and transforming growth factor-β signaling pathways [56]. At environmentally relevant doses, BPA enhanced cell proliferation, induced cyclooxygenase-2 (COX-2) gene expression, and promoted cell migration and invasiveness [57]. BPA induced proliferation in immortalized human UF cells through membrane-associated ERα36 by the activation of Src, epidermal growth factor receptor, Ras, and microtubule affinity regulating kinase pathways [58]. Most of these *in vitro* studies indicated that BPA increased the proliferation of human UF cells, possibly contributing to UF growth.

2. Phthalates

The NHANES from 1999–2004 showed a positive association between a specific phthalate metabolite (MBP) and the risk of UFs. However, other metabolites (MEHP, MEHHP, and MEOHP) were inversely associated with UFs [43]. Women with UFs exhibited significantly higher levels of total urinary MEHP than those in healthy controls [59]. In one population-based study conducted in Korea, the urinary concentration of 16 phthalate metabolites was compared in women with and without UF. Using multiple logistic regression analyses, a significant association was found between the levels of total urinary DEHP metabolites and UF [60]. Recently, in the USA, a cross-sectional study on premenopausal women seeking surgical care for UFs showed elevated urine concentrations of several phthalates, which were positively associated with the uterine volume. In particular, these effects were more prominent for DEHP metabolites [61].

In vitro treatment of DEHP promoted cell viability, proliferative activity, and anti-apoptotic activity in human leiomyoma cells. Furthermore, DEHP treatment on human UF cells increased hypoxia inducible factor 1α and COX-2 expression, which may be involved in inflammatory response [62]. These findings suggest an association between phthalate exposure and UF. Despite the importance of these reports, additional phthalates should be tested for association with UFs.

Polycystic ovarian syndrome

PCOS is one of the most common ovulatory disorders with

hyperandrogenemia and/or insulin resistance. Recently, there is emerging evidence about the effect of npEDCs on PCOS, especially BPA. However, data regarding the impact of phthalate, TCS, and paraben exposure on PCOS are very limited.

1. Bisphenol A

After a positive relationship between androgen concentration and BPA in women with ovulatory dysfunction has been suggested [63], a case control study (71 women with PCOS and 100 women without PCOS) found that serum BPA was significantly higher in PCOS women and that there was a significant positive association between BPA, androgen concentration, and insulin resistance [64]. Furthermore, PCOS women with higher serum BPA had more severe insulin resistance, increased free androgen index, and increased markers of chronic inflammation [65]. Market seller women with PCOS exhibited higher serum BPA levels than non-PCOS women [66]. According to a recent meta-analysis, PCOS patients had significantly higher BPA levels than those of control groups (standardized mean difference, 2.437; 95% CI, 1.265–3.609, $P<0.001$) [67]. These results suggest a role of BPA in the development and/or pathogenesis of PCOS.

BPA may act on ERs to mimic actions like estrogen and may bind to membrane receptors to cause harmful effects even at pico- and nanomolar concentrations. Rutkowska and Diamanti-Kandarakis [68] summarized the molecular effect of BPA on PCOS as altering ovarian steroidogenesis, aggravating hyperandrogenism state, altering oocyte development and folliculogenesis, and worsening metabolic parameters such as insulin resistance, obesity, oxidative stress, and inflammation.

2. Phthalates

PCOS patients have significantly lower urinary concentrations of monobenzyl phthalate (mBzP), and low urine concentrations of mBzP and MBP increase the likelihood of PCOS (OR, 0.14–0.25; $P<0.05$). This result only showed that PCOS patients may differ from controls in their environmental contaminant profile but failed to show a positive correlation between phthalate and PCOS [69]. In order to verify the impact of antenatal exposure to phthalates on the development of PCOS in the descendants, a study in the context of the Western Australian Pregnancy Cohort (Raine) Study assessed the most common phthalate metabolites in 3,000 pregnant women. This study showed antenatal exposure to phthalates had some protective effects on the development of PCOS which implicated long-term effects of phthalates on reproduction [70]. In contrast to these results, one study suggested that gestational exposure to some phthalates (dibutyl phthalate and DEHP) results in polycystic ovaries and hormonal profiles similar to PCOS [71]. To summarize, only limited and contradictory results are available regarding the effect of phthalates on PCOS.

3. Parabens and triclosan

In a cross-sectional study in Chinese infertile women, patients with PCOS exhibited significantly higher TCS concentrations than those in control women (median of TCS (IQR), μg/g creatinine: 1.49 (0.68–3.80) vs. 1.06 (0.52–3.02), $P=0.0407$). Compared to the lowest tertile, the highest tertile of TCS concentration was associated with an increased odds of PCOS (OR, 1.99; 95% CI, 1.05–3.79) [72]. In contrast, a case-control study exploring the association between the urinary concentration of personal care products and PCOS found no significant differences in TCS detection rate or the total concentration of analytes [73].

Infertility and/or subfertility

Female infertility is a complex disorder that can be caused by anatomic, genetic, environmental, and endocrine factors. The comprehension of npECD mechanisms of action, as well as the presumed risks deriving from the exposure to these compounds, may be crucial to improve women's fertility.

1. Bisphenol A

Numerous studies have investigated the effect of BPA on women infertility. BPA is associated with women infertility by affecting the morphology and functions of the oviduct, uterus, and ovary [74]. Furthermore, BPA affects the hypothalamus-pituitary-ovarian function by altering the secretion of gonadotropin-releasing hormones in the hypothalamus and promoting pituitary proliferation [75]. The Shanghai Birth Cohort Study investigated the impact of BPA exposure on fecundability in healthy women. Each one-unit increase in urinary concentrations of BPA was associated with a 13% reduction in fecundability (fecundability OR, 0.87; 95% CI, 0.78–0.98) and a 23% increase in the odds of infertility

Table 1. The evidences of reproductive health-related actions of nonpersistent endocrine disrupting chemicals (npEDCs) on human

Study	Total number (case/control)	Country	Study design	Compounds	Sample	Main results
Menstrual cycle						
Jukic et al. [14]	221	USA	Prospective cohort	BPA	Urine	Shorter luteal phase in higher quartile patients (P=0.001) (2nd vs. 1st: –0.8 days [95% CI, –1.2, –0.4], 3rd vs. 1st: –0.4 days [95% CI, –0.8, 0.02])
				MCOP	Urine	Shorter luteal phase in higher quartile patients (P=0.040); (2nd tertile vs. 1st tertile: –0.5 days [95% CI, –0.9, –0.1], 3rd vs. 1st: –0.4 days (95% CI, –0.8, 0.01])
				BPA and phthalate metabolites	Urine	No association with follicular-phase length (P>0.05)
Nishihama et al. [23]	128	Japan	Cross-sectional	Parabens	Urine	Negative association with menstrual cycle length (OR, 0.73; 95% CI, 0.56, 0.96) and butyl paraben concentrations (OR, 0.83; 95% CI, 0.70, 0.99)
Pollack et al. [15]	143	USA	Prospective cohort	BPA and parabens	Urine	Associated with increased serum estradiol in multi-chemical models (P<0.05) (OR, 0.21; 95% CI, 0.15, 0.28 and OR, 0.12; 95% CI, 0.07, 0.15)
Endometriosis						
Cobellis et al. [38]	79 (55/24)	Italy	Case-control	DEHP	Serum	Higher plasma DEHP concentrations in patient group (P=0.005)
Reddy et al. [40]	220 (85/135)	India	Case-control	Phthalate esters	Serum	Significantly higher in stage I to IV endometriosis patients (P<0.05)
Itoh et al. [35]	140	Japan	Cross-sectional	BPA	Urine	No difference in women with stage 0–I endometriosis (0.74 μg/g creatinine) and II–IV endometriosis (0.93 μg/g creatinine) (P=0.24)
Cobellis et al. [30]	69 (58/11)	Italy	Case-control	BPA, BPB	Serum	Highly detected in endometriosis patients (P<0.05)
Itoh et al. [45]	137 (57/80)	Japan	Cross-sectional	Phthalate metabolites	Urine	No monotonic trend was seen in phthalate metabolites by endometriosis stage (P=0.23–0.90)
Weuve et al. [43]	1,227	USA	Cross-sectional	MBP	Urine	Weakly associated with increased odds of endometriosis (highest vs. lowest 3 quartiles: OR, 1.36; 95% CI, 0.77, 2.41)
Kim et al. [39]	266 (97/169)	Korea	Case-control	MEHP	Serum	High plasma levels of MEHP in advanced stage endometriosis patients (OR, 1.02; 95% CI, 1.003, 1.038)
				DEHP	Serum	High plasma levels of DEHP in advanced stage endometriosis patients (OR, 1.001; 95% CI, 1.000, 1.002)
Buck Louis et al. [34]	600 (473/127)	USA	Matched-cohort	Phthalate metabolites	Urine	Phthalate metabolites were associated with a 2-fold increase in the odds of an endometriosis diagnosis (OR, 1.23; 95% CI, 0.88, 1.72)
Upson et al. [44]	287 (92/195)	USA	Population-based case- control	MEHP	Urine	Strong inverse association between urinary MEHP concentration and endometriosis risk (OR, 0.3; 95% CI, 0.1, 0.7)
Upson et al. [31]	430 (143/287)	USA	Case-control	BPA	Urine	Positive associations with non-ovarian pelvic endometriosis (OR, 3.0; 95% CI, 1.2, 7.3)
Simonelli et al. [33]	128 (68/60)	Italy	Case-control	BPA	Urine	Statistically higher levels in patients (P=0.02) (5.31±3.36 vs. 1.64±0.49 pg/μL)

Table 1. Continued.

Study	Total number (case/control)	Country	Study design	Compounds	Sample	Main results
Rashidi et al. [32]	100 (50/50)	Iran	Case-control	BPA	Urine	Positive association between endometrioma and BPA level (OR, 1.74; 95% CI, 1.40, 2.16)
Uterine fibroids						
Weuve et al. [43]	1,227	USA	Cross-sectional	MBP	Urine	Weakly associated with increased odds of leiomyoma (highest vs. lowest 3 quartiles: OR, 1.56; 95% CI, 0.93, 2.61)
				MEHP	Urine	Inversely associated with leiomyoma (highest vs. lowest 3 quartiles: OR, 0.63; 95% CI, 0.35, 1.12).
Huang et al. [59]	65 (36/29)	Taiwan	Case-control	MEHP	Urine	Significantly higher levels in patients (P<0.05)
Shen et al. [51]	262 (156/106)	China	Case-control	BPA	Urine	Significantly higher levels in patients (P<0.05) (11.79±1.74 vs 17.56±2.33 ng/mL)
Zhou et al. [52]	78 (49/29)	China	Case-control	BPA	Urine	Significantly higher levels in patients (P<0.05) (13.9±12.7 vs 8.50±12.2 ng/mL)
Kim et al. [60]	57 (30/27)	Korea	Case-control	Sum of phthalate metabolites	Urine	Significantly higher levels in patients (OR, 10.82; 95% CI, 1.28, 93.46)
Zota et al. [61]	57	USA	Cross-sectional	Sum of phthalate metabolites	Urine	Positive association between uterine volume and phthalates (33% difference; 95% CI, 6.6, 66.4)
Polycystic ovarian syndrome						
Kandaraki et al. [64]	171 (71/100)	Greece	Case-control	BPA	Serum	Significantly higher levels in the total PCOS group (P<0.001) (1.05±0.56 vs. 0.72±0.37 ng/mL)
Vagi et al. [69]	102 (52/50)	USA	Case-control	Phthalate metabolites	Urine	Lower concentrations in PCOS group (P<0.05; OR, 0.14, 0.25)
Vahedi et al. [66]	124 (62/62)	Iran	Case-control	BPA	Serum	Significantly higher levels in PCOS group (P<0.05) (0.48±0.08 vs. 0.16±0.04 ng/mL)
Infertility						
Alur et al. [81]	750	USA	Prospective cohort	Sum of phthalate metabolites	Urine	No difference between women with a history of infertility and the comparison group Lower in women who conceived after ART (geometric mean ratio, 0.83; 95% CI, 0.71, 0.98)
Messerlian et al. [80]	215	USA	Prospective cohort	Sum of phthalate metabolites	Urine	Higher urinary concentrations of phthalate metabolites were significantly decreases in mean antral follicle count (P<0.05)
Smarr et al. [83]	501	USA	Prospective cohort	Paraben	Urine	Highest quartile of MP concentrations relative to the lowest, a 34% reduction in fecundity (aFOR, 0.66; 95% CI, 0.45, 0.97)
Wang et al. [76]	700	China	Prospective cohort	BPA	Urine	Associated with a 13% reduction in fecundability (FOR, 0.87; 95% CI, 0.78, 0.98) Association with a 23% increase in odds of infertility (OR, 1.23; 95% CI, 1.00, 1.50)

BPA, bisphenol A; BPB, bisphenol B; MCOP, monocarboxyoctyl phthalate; DEHP, di-2-ethylhexyl-phthalate; MEHP, monoethylhexyl phthalate; MBP, monobutyl phthalate; MP, methyl paraben; OR, odds ratio; CI, confidence interval; RDS, relative standard deviation; FOR, fecundability odds ratio.

(OR, 1.23; 95% CI, 1.00–1.50). In addition, these associations were strengthened among women over 30 years of age [76].

Recently, because of the potential harmful effects of BPA, many countries replaced BPA with the analogs bisphenol S (BPS) and bisphenol F (BPF). The products containing these analogs are known as 'BPA-free products'. However, several *in vitro* and *in vivo* studies demonstrated that BPS and BPF also exert the same endocrine disrupting effects as BPA [77]. Regarding oocyte maturation, both BPA and BPS caused significant spindle abnormalities and chromosome misalignment, even at very low doses [78]. Both epidemiological and experimental evidence demonstrates that all bisphenol affects female infertility and/or subfertility.

2. Phthalates

The *in vitro/vivo* effects of phthalates on various reproductive organs have been extensively studied [20,21,48,79]. The relevance of these results to humans is still controversial. In women with infertility, urinary phthalates were found associated with decreased antral follicle count, which may lead to decreased fecundity [80]. In contrast, another study in women with a history of infertility did not show any difference in the concentrations of urinary phthalate metabolites [81]. A systematic review summarizing the evidence of the associations between common npEDCs and fecundability, and between phthalate exposure and time to pregnancy (TTP), only reported equivocal associations [82]. The studies on the effects of phthalates on fertility yielded heterogeneous results. These inconsistencies may be related to study designs and to the characteristics of the examined populations.

3. Parabens and triclosan

The Longitudinal Investigation of Fertility and the Environment (LIFE) study, which included 501 couples of reproductive age recruited in Michigan and Texas from 2005 and 2009, showed that exposure to high levels of methyl paraben and ethyl paraben was associated with reduced TTP [83]. According to LIFE study, exposure to parabens with longer TTP has been suggested. However, no effect of TCS on fecundability has been demonstrated [82].

Conclusion

The majority of the available data strengthen the evidence of reproductive health-related impact of npEDCs and we have summarized the published results about human on Table 1. Several animal studies and *in vitro* studies have shown that exposure to npEDCs can alter reproductive functions. However, the exact mechanisms by which npEDCs cause physiological, cellular, and molecular changes in women's reproductive health are not clear. Adverse effects can be caused by low-dose exposure and characterized by a non-linear dose response. Notably, these effects are not limited to the female reproductive age and can occur throughout the lifespan or through the generation. Recommendations should be made in order to reduce human exposure to npEDCs and to protect future generations from steadily increasing reproductive health risks.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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