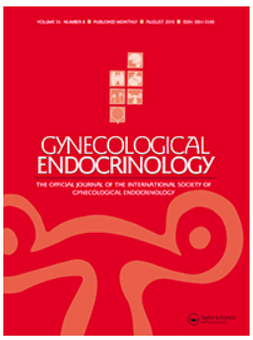

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ENDOMETRIOSIS AND EXPOSURE TO ENDOCRINE-DISRUPTING CHEMICALS

The risk of endometriosis after exposure to endocrine-disrupting chemicals: a meta-analysis of 30 epidemiology studies

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ABSTRACT

Endocrine-disrupting chemicals (EDCs) are suspected to be associated with endometriosis (EMs). This study aimed to synthesize published data and evaluate the relationship between four classic EDCs exposure and the risk of EMs. A systematic literature search for original peer reviewed papers was performed in the databases PubMed, EMBASE, and Web of Science based on inclusion criteria up to January 2018. Subsequently, a total of 20 papers conducting 30 studies fulfilled the eligibility criteria and were included in this meta-analysis (four studies for bisphenol A (BPA), 12 studies for polychlorinated biphenyls (PCBs), eight studies for organochlorine pesticides (OCPs), and six studies for phthalate esters (PAEs)). The overall odds ratio (OR) across all exposures and EMs was 1.41 (95% confidence interval (CI): 1.23–1.60). When assessing four specific chemicals, respectively, consistent increases in the risk of EMs were found in PCBs group (OR = 1.58; 95% CI: 1.18–2.12), OCPs group (OR = 1.40; 95% CI: 1.02–1.92) and PAEs group (OR = 1.27; 95% CI: 1.00–1.60), while BPA showed no significant association with EMs. Besides, in the di-(2-ethylhexyl)-phthalate (DEHP) group – the most commonly used PAEs, significant risk was also found (OR = 1.42; 95% CI: 1.19–1.70). The current meta-analysis strengthens the evidence that specific EDCs or their metabolites may promote the occurrence of EMs.

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Introduction

Endometriosis (EMs) is defined as the presence of endometrial-type mucosa outside the uterine cavity. EMs appear to be one of the most common benign gynecological diseases in premenopausal women with morbidity 10–15% of reproductive aged women and 30–50% in women with infertility [1]. Moreover, EMs are associated with increased risk of epithelial ovarian cancer [2]. Although the underlying pathogenesis of EMs still remains unclear, the environmental factors seem likely to play a role.

Endocrine-disrupting chemicals (EDCs) have been described as a general class of chemicals that induce hormone dysregulation in humans or wildlife, exerting adverse effects on reproductive, developmental, cardiovascular, neurological, metabolic, and immune process [3]. Human exposure to EDCs has aroused a wide range of health concerns, including obesity, diabetes, cancer, and decreased fertility [4–8].

Classic EDCs such as bisphenol A (BPA), polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs), and phthalate esters (PAEs) were all suspected to impair human reproductive system and have been associated with several gynecological diseases such as polycystic ovarian syndrome, spontaneous abortion, primary ovarian failure, and EMs [3]. BPA is a monomer widely used to synthesize plastic materials, which is usually present in the surface coating of food cans, food packaging, plastic bottles, and children toys [9]. Animal studies have found that pre-natal exposure of mice to BPA can elicit an EM-like phenotype in female offspring [10]. PCBs are a class of industrial chemical mixtures of 200 or more congeners that were mass-produced globally from 1920s, which was found to significantly enhance the growth of endometrial lesions in mice [11]. Although the production of PCBs has been banned in the late 1970s, it can still be detected in polluted air, water, soil, fish or other species due to their lipophilicity and bioaccumulation characteristics [12–14]. OCPs are a class of compounds which were globally produced and used in the last century. Due to their highly lipophilic characteristics, OCPs accumulate to high levels in fatty tissues of human organs via food chain and cause comprehensive toxic damages, including neurotoxicity, immunotoxicity, hepatotoxicity, and genital toxicity [15–17]. PAEs are a group of synthetic chemicals which were commonly used as plasticizers in the manufacturing of flexible polyvinyl chloride products [18], of which, the most commonly used di-(2-ethylhexyl)-phthalate (DEHP), is also known as a widespread environmental contaminant [19]. It was suggested by *in vitro* studies that DEHP could increase reactive oxygen species (ROS) generation and decrease expression of superoxide dismutase (SOD), and induce estrogen receptor-α expression in a dose-dependent manner, which may be associated with the development of endocrine-related disease such as EMs [20].

For the past few years, several epidemiologic investigations have reported the adverse effect of EDCs exposures on the risk of EMs, nevertheless, there are also studies indicating that there is no enough evidence to support the conclusion. We thus did a meta-analysis to summarize the evidence on EMs risk that has been studied in its association with exposure of four classic

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Supplemental data for this article can be accessed here.

EDCs: BPA, PCBs, OCPs, and PAEs, thus help to provide a better understanding of the impact of EDCs on EMs.

Methods and materials

Literature search

PubMed, EMBASE, and Web of Science databases were systematically searched for relevant studies published before January 1 2018. Detailed search strategies are presented in Supplemental Table S1. No publication date or article types were restricted. Bibliographies of all relevant articles and reviews were also checked manually for potential studies. Literature search was conducted by two independent authors.

Study selection

We selected studies according to the following inclusion criteria: (a) written and published in English; (b) case-control studies, cohort studies or cross-sectional studies; (c) studies evaluating the association between exposure of above four EDCs and risk of EMs; (d) an odds ratio (OR) with 95% confidence interval (CI) was reported, or could be calculated from provided data; Studies were excluded from the meta-analysis if they: (a) were experimental articles, meta-analyses, letters, reviews, or editorial articles; (b) did not published as full reports; (c) included subjects that were already reported in another more complete or more recent study. If the same author using the same patient population published more than one study or overlapping case series, the study with the largest sample size was included.

Data extraction and qualitative assessment

Descriptive information was recorded from each publication. For each study, first author's name, publication year, original country, study design, control source, sample size, exposure medium, the specific EDCs or their metabolites analyze, and the risk estimates with 95% CI were extracted. A modification of the Newcastle-Ottawa Scale (NOS) was used to assess quality of case-control studies and cohort studies for three aspects: the selection of study groups, comparability of groups, and ascertainment of either the exposure or outcome of interest. Cross-sectional study was assessed by using Agency for Healthcare Research and Quality (AHRQ) with 11-item checklist. Quality was assessed by two independent authors. Article quality was classified as follows: for case-control and cohort studies, low quality = 0–4; moderate quality = 5–6; high quality = 7–9, and for cross-sectional study, low quality = 0–3; moderate quality = 4–7; high quality = 8–11.

Statistical analyses

The risk for EMs associated with four types of EDCs exposure was quantitatively estimated by calculating ORs with 95% CIs. We used the most-adjusted ORs to synthesize the summary OR. In order to unify different studies on a comparable scale, a common cutoff based on original studies was adopted and categories of EDCs concentrations in each study were regrouped respectively into two, representing medium or high level of exposure. When more than one category (e.g. 3rd and 4th quartile categories) in a study were provided at the same time, we used the Hamling et al. [21] method to pool the corresponding estimates, and used the pooled estimates for this meta-analysis. When studies provided ORs separately for different subtypes of the specific EDCs, inverse-variance method was used to recalculate the pooled OR as described previously [22,23]. Heterogeneity of effects across studies was assessed by Cochran's Q and I^2 test statistic, and was deemed significant when $p<.10$ or $I^2>50\%$, and then random-effects models were chosen to calculate summary OR and 95% CI, otherwise we chose fixed-effects models. Begg's funnel plot and Egger's regression test were used to exclude the possibility that publication bias may affect the results. When $p>.05$, it was considered no evidence of publication bias. Meta-regression analysis was also performed to evaluate the source and weight of heterogeneity by type of EDCs exposure, ethnicity, study design, source of controls, exposure medium, and study quality. Analyzed factor was defined as one source of heterogeneity when $p\leq.05$. To assess the stability of pooled OR, sensitivity analysis was conducted by excluding one study at a time. Stratified analyses were also conducted by study design, control source, and ethnicity. Moreover, we also estimated OR of DEHP and EMs. We chose its primary metabolite: mono-(2-ethylhexyl) phthalate (MEHP) and four secondary oxidized metabolites: mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), and mono-[2-(carboxymethyl) hexyl] phthalate (MCMHP) as representatives of DEHP exposure since they are more sensitive to detection and account for approximately 75% of DEHP metabolites [24]. All analyses were conducted by using STATA version 12.0 (STATA Corporation, College Station, TX).

Results

Characteristics of included studies

A total of 431 articles were preliminarily identified after our initial search. After removing duplicates, we obtained 159 hits in total. Two authors browsed titles and abstracts independently to assess eligibility and retrieved 43 papers to acquire full texts. Hand searching of the bibliographies of relevant articles and reviews did not capture additional analysis. We preliminarily selected 22 papers meeting inclusion criteria; however, two of 22 papers did not provide risk estimates with OR and 95% CI [25,26], thus the two studies were eliminated. For the present meta-analysis, we finally identified 20 papers that conducted 30 independent studies (contributing 64 risk estimates between EDCs or their metabolites and risk of EMs), including 21 case-control [27–43], eight cohort [44,45], and one cross-sectional study [46]. We retrieved six separated investigations from three articles [41,44,45] since different control source or case groups were studied simultaneously. Moreover, seven studies [39,41,44,45] researched more than one EDC, we treated these studies as separated research groups. Flowchart of the process for study identification and selection is shown in Figure 1. Detailed information on each study is summarized in Supplemental Table S2. Quality assessment was depicted in Supplemental Table S3, the quality of all included studies was acceptable with score range 5–8.

Association of EDCs exposure and risk of EMs

Thirty studies providing a total of 64 OR estimators were accepted in the current meta-analysis. The total OR for risk of EMs associated with exposure to four EDCs was 1.41 (95% CI:

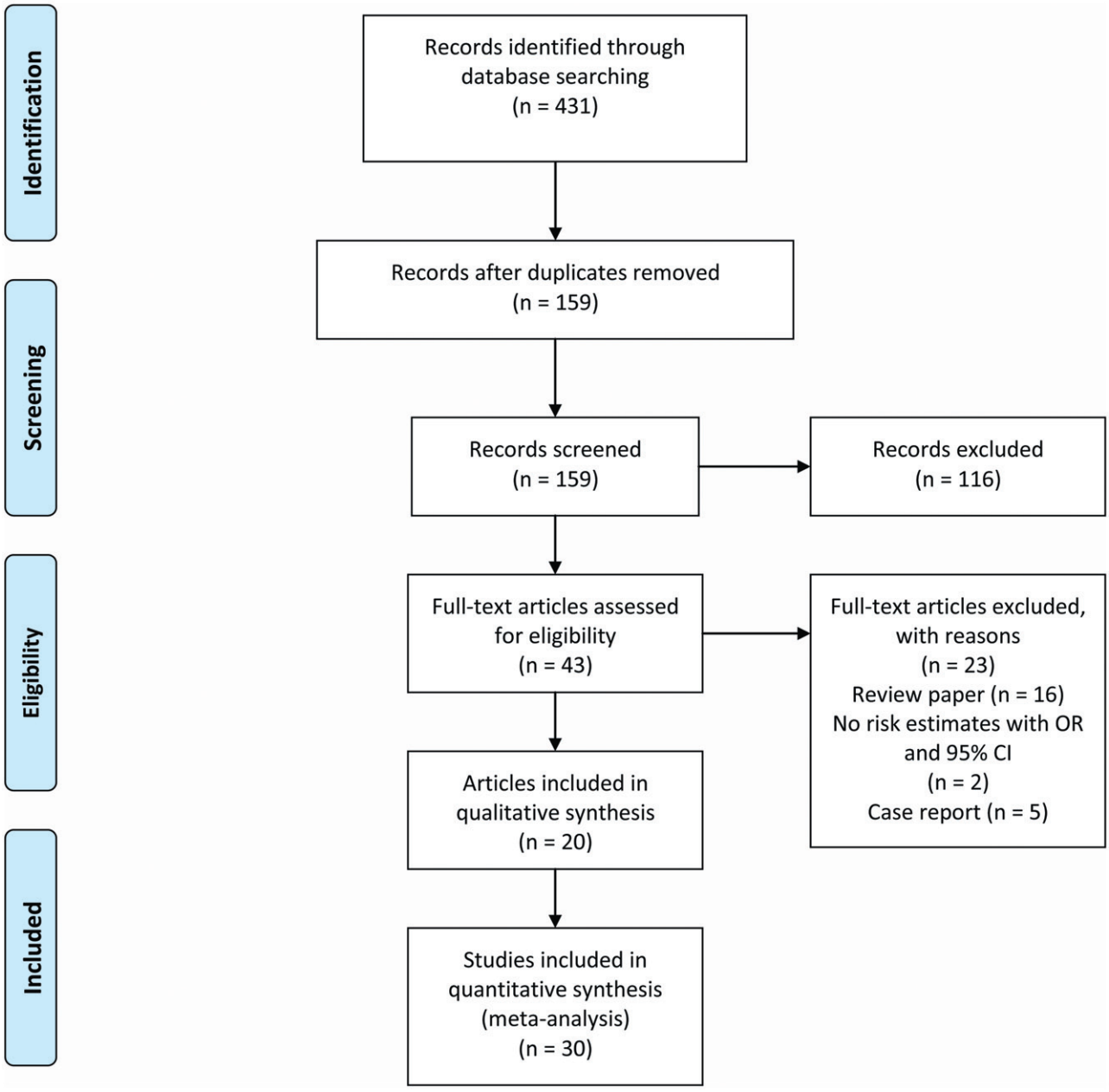

Figure 1. Flowchart of the process for study identification and selection.

1.23–1.60) by random-effects models as shown in forest plot (Supplement Figure 1). Result of heterogeneity test using Cochran's Q and I^2 statistic was $p< .10$ and I^2=88.7%, respectively, indicating the existence of heterogeneity. Results of sensitivity analysis by omitting one study at a time indicated none of single study substantially changed the corresponding pooled OR and 95% CIs (Supplement Figure S2A), which indicated our result was relatively stable and credible. Begg's funnel plot and Egger's regression test indicated no evidence of publication bias with p=.16 (Supplement Figure S3A). Moreover, results of meta-regression analysis showed that control source, ethnicity and study quality were the sources of heterogeneity, which contributed 13.89%, 22.14%, and 19.57% of the τ^2 value, respectively, indicating that control source, ethnicity and study quality could only explain one part of the heterogeneity observed in the current study (Table 1, Supplement Figure S4). For the analyses of specific EDC, significant associations were found between PCBs (OR = 1.58; 95% CI: 1.18–2.12), OCPs (OR = 1.40; 95% CI: 1.02–1.92), PAEs (OR = 1.27; 95% CI: 1.00–1.60), and EMs (Supplement Figure S1), and for the most common used PAEs–DEHP, significant association was also found (OR = 1.42; 95% CI: 1.19–1.70) (Supplement Figure S5). Furthermore, Begg's funnel plot and Egger's regression test showed no evidence for publication bias with p=.17 (Supplement Figure S3B), and the result of sensitivity analysis indicated the pooled OR was stabilized as shown in Supplement Figure S2B. In subgroup analysis based on control source, study design and ethnicity, several positive results were also found (Table 2). However, given the limited amount of included studies in each subgroup, the results should be explained cautiously.

Discussion

A substantial proportion of published documents have reported the correlation between EDCs exposure and the pathogenesis of

EMs from animal toxicological studies, cellular experiments, and human studies [10,29,47,48]. However, the conclusions of epidemiology studies were inconsistent. Taking BPA for example, in 2013, Buck Louis et al. [44] first explored the correlation between urinary BPA levels and EMs in both operative cohort and population cohort, nevertheless, no significant result was found (ORs for operative cohort and population cohort were 0.96, 95% CI: 0.79–1.19 and 1.68, 95% CI: 0.96–2.92, respectively). In the following year, Upson et al. [27] conducted a similar study and the results suggested that increased urinary BPA levels were associated with an increased risk of non-ovarian pelvic EM, but not ovarian EM (ORs of third quartiles compared with first quartiles were 1.10, 95% CI: 0.50–2.50 and 3.00, 95% CI: 1.10–7.60 for ovarian EM and non-ovarian pelvic EM, respectively). And then, in 2017, study by Rashidi et al. [28] showed a positive association between urinary BPA concentrations and EMs (OR = 1.74; 95% CI: 1.40–2.16). These contradictory results indicated that BPA was a potential risk factor of EMs whereas the conclusion needs to be validated by more well-designed studies. Similarly, studies regarding association between PCBs, OCPs, PAEs and EMs were also inconclusive. Hence, a systematic meta-analysis summarizing previous study results is required.

In this meta-analysis, we first evaluated the epidemiological evidence on classic EDCs exposure (BPA, PCBs, OCPs, and PAEs) and female reproductive disorder – EMs, based on 30 independent studies from North America (16 studies), Asia (six studies), and Europe (eight studies). On the whole, our results suggested all PCBs (OR = 1.58; 95% CI: 1.18–2.12), OCPs (OR = 1.40; 95% CI: 1.02–1.92), PAEs (OR = 1.27; 95% CI: 1.00–1.60), and DEHP (OR = 1.42; 95% CI: 1.19–1.70) were risk factors of EMs, which were consistent with several reported *in vivo* animal studies and *in vitro* studies [11,20]. While no significant association was observed between BPA (OR = 1.40; 95% CI: 0.94–2.08) and EMs for the current study. However, considering the limited number of studies in each category, cautions should be paid in the interpretation of these results. We speculated the negative outcome of BPA was attributed to the small size of analyzed studies (four studies). Since small sample with limited participants was often accompanied with selection biases [49], the result of BPA and EMs remains to be confirmed by well-designed epidemiology studies.

Heterogeneity was existed in the current meta-analysis, however, the results of meta-regression analysis could only explain one part of the heterogeneity observed in this study by control source, ethnicity and study quality, suggesting heterogeneity might be explained by other confounding factors. Other possible source of heterogeneity might be as follows: (1) mean age of objects. Since age is associated with both stages of EMs and exposure duration of EDCs, diversity of mean age in included studies may engender inconsistent results [50]. However, in this meta-analysis, age distribution in most studies was decentralized, and quite a part of studies did not provide mean age of subjects, which made it difficult to analyze heterogeneity resulted from this factor. (2) Sub-types of EMs. Pathogenic hypothesis supported by the most robust evidence is based on the so-called retrograde menstruation phenomenon [51]. However, this hypothesis may partially explain occurrence of EMs within ovary but fails to explain the presence of deep infiltrating EMs or other remote sites outside the peritoneal cavity [52]. Since it is yet unknown whether exposure of EDCs has a relationship with sub-types of EMs, separating cases into subgroup according to sub-types of EMs is the most-complete design solution to eliminate this interference. However, in this meta-analysis, only two included studies [27,41] divided case group into non-ovarian pelvic EM group and ovarian EM group. (3) Co-exposure of other EDCs. To our knowledge, humans are exposed to a mixture of chemicals rather than a single chemical [53]. Since the pathogenic mechanism and targets of different EDCs differ from each other, co-exposure of EDCs may exacerbate toxicological effect [54–56]. Toxicological studies have reported that co-exposure of EDCs performed reproduction toxicity in animals below the no-

Table 1. Meta-regression results of association between EDCs exposure and EMs risk.

Covariates	Coef.	Std. err.	*p*	95% CI
Type of EDCs				
BPA	0.124	0.351	0.728	−0.598 to 0.846
PCBs	0.0778	0.259	0.766	−0.454 to 0.610
Pesticides	0.128	0.236	0.593	−0.357 to 0.613
PAEs	Referent	Referent	Referent	Referent
Study design				
CCS	0.612	0.596	0.314	−0.612 to 1.836
CS	0.163	0.588	0.783	−1.044 to 1.371
CSS	Referent	Referent	Referent	Referent
Control source	**0.117**	**0.239**	**0.003**	**0.040–0.196**
Ethnicity	**0.173**	**0.142**	**<0.001**	**0.079–0.223**
Study quality	**−0.194**	**0.256**	**0.002**	**0.064–0.210**
Exposure medium				
Urinary	0.284	0.342	0.413	−0.417 to 0.985
Serum	0.294	0.280	0.304	−0.281 to 0.867
Fat	Referent	Referent	Referent	Referent

EDCs: endocrine-disrupting chemicals; BPA: bisphenol A; PCBs: polychlorinated biphenyls; OCPs: organochlorine pesticides; PAEs: phthalate esters; CCS: case-control study; CS: cohort study; CSS: cross-sectional study.
Bold values are statistically significant ($P < 0.05$).

Table 2. Stratified analyses of EDCs and EMS by control source, ethnicity, and study design.

Variables	BPA N/OR(95% CI)/I^2 %/P_Q	PCBs N/OR(95% CI)/I^2 %/P_Q	OCPs N/OR(95% CI)/I^2 %/P_Q	PAEs N/OR(95% CI)/I^2 %/P_Q
Overall	4/1.40(0.94, 2.08)/82/0.001	**12/1.58(1.18, 2.12)/84/<10^{-3}**	**8/1.40(1.02, 1.92)/94/<10^{-3}**	**6/1.27(1.00, 1.60)/86/<10^{-3}**
Control source				
Hospital	2/1.29(0.72, 2.31)/94/<10^{-3}	**9/1.74(1.21, 2.51)/88/<10^{-3}**	6/1.38(0.87, 2.20)/96/<10^{-3}	5/1.18(0.96, 1.45)/70/0.009
Population	**2/1.61(1.03, 2.52)/0/0.811**	3/1.29(0.93, 1.78)/0/0.515	2/1.31(0.95, 1.80)/70/0.069	**1/1.62(1.35, 1.95)**
Ethnicity				
Asian	**1/1.74(1.40, 2.16)**	1/0.75(0.38, 1.48)	1/0.41(0.14, 1.24)	**3/1.44(1.18, 1.76)/0/0.780**
Caucasian	3/1.23(0.82, 1.84)/54.1/0.119	**11/1.69(1.25, 2.30)/85/<10^{-3}**	**7/1.50(1.08, 2.07)/95/<10^{-3}**	3/1.13(0.80, 1.59)/92/<10^{-3}
Study design				
CCS	**2/1.72(1.40, 2.12)/0/0.707**	**10/1.78(1.31, 2.42)/66/0.002**	**6/1.51(1.07, 2.13)/90/<10^{-3}**	**3/1.44(1.18, 1.76)/0/0.780**
CS	2/1.19(0.70, 2.04)/0/0.907	2/0.97(0.88, 1.06)/0/0.406	2/1.18(0.68, 2.05)/90/0.001	2/1.27(0.80, 2.02)/96/<10^{-3}
CSS	–	–	–	1/0.86 (0.64, 1.16)

N: number of study; P_Q: *p* values of the *Q*-test for heterogeneity test; EDCs: endocrine-disrupting chemicals; BPA: bisphenol A; PCBs: polychlorinated biphenyls; OCPs: organochlorine pesticides; PAEs: phthalate esters; CCS: case-control study; CS: cohort study; CSS: cross-sectional study.
Bold values are statistically significant ($P < 0.05$).

observed-adverse-effect level of each EDC individually [57–59]. However, at present, this factor is unpredictable and uncontrollable in human beings.

There are some limitations in the current study. First, the number of included studies was small, and only published papers in English were included, which means a part of negative results do not get published or published in non-English journals would not be included in the meta-analysis [60,61]. Second, co-exposure was controlled in none of 30 studies, which might obscure the true correlation between one specific EDC exposure and EMs. Third, most studies just collected single spot specimen (serum or urine), which might be not enough to reflect internal EDCs exposure during previous months or even years period. Especially for BPA, whose half-life time in human body is only 5.4 h [62]. Thus, a more appropriate detection for EDCs exposure should be collecting multiple spot urine samples on different days instead of single spot urine. Fourth, the control groups in 22 out of 30 studies were composed of subfertile women rather than general population. Since EDCs are potential risk factors for several female reproductive disorders not only EMs, but also PCOS, miscarriage, premature deliveries, and so on [63–65], it is better to establish control group consisting of normal people, thereby excluding interference of related diseases.

Key strengths of this meta-analysis in comparison with previous studies or reviews are: (1) it includes, to our knowledge, all published epidemiological evidence fulfilling inclusion criteria regarding relationship between exposure of BPA, PCBs, OCPs, PAEs and incidence of EMs for the first time; (2) for the most common PAEs–DEHP, we also investigated its association with EMs; (3) comprehensive stratified analyses based on study design, control source and ethnicity were conducted, and several positive associations were found.

In summary, despite several possible limitations, this systematical meta-analysis based on a total of 30 studies demonstrated that EDCs exposures do have connection with incidence of EMs for the first time. Future research is needed for a deep exploration in the followings: (1) the biomarkers of EDCs exposure should be well defined, and the detection of EDCs needs to be normalized; (2) adequate samples size, occupational exposure, longitudinal investigation, and multi-center clinical studies need to be conducted; (3) mechanism studies focused on exposure dose, exposure duration and exposure phase of EDCs should be emphasized; (4) co-exposure of EDCs should be controlled, and their interactions should be investigated to make the epidemiology evidence more credible.

Disclosure statement

No potential conflict of interest was reported by the authors.

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