

## Human Exposure to Polychlorinated Biphenyls (PCBs) and The Risk of Endometriosis: A Systematic Review and Meta-Analysis Protocol

### Abstract

Endometriosis is one of the gynecological disorders and its prevalence is estimated to 8-10% of reproductive-age women. In Iran, the frequency of endometriosis was reported at 29% among infertile women. The etiology of endometriosis is still unclear. Numerous environmental contaminants such as polychlorinated biphenyls (PCBs) may play important roles in endometriosis development and etiology. Iranian population has relatively low levels of PCBs. However, no studies have evaluated PCBs levels in Iranian endometriosis patients so far. At present, there is no systematic review of the relationship between only PCBs exposure and the risk of endometriosis. The aim of this systematic review and meta-analysis protocol will be to evaluate the association between only PCBs exposure and the risk of endometriosis. PubMed/MEDLINE, Web of Science, Scopus, Google Scholar, Embase, key journals, conferences/congress research papers, and the references of included primary studies will be searched. Observational studies (cross-sectional, case-control, and cohort) in humans that investigated the association between PCBs exposure and the risk of endometriosis will be included. The outcome will be endometriosis risk in association with PCBs exposure. The primary screening and data extraction will be performed by three team members independently and will be judged by opinion with the fourth member. The modified Newcastle-Ottawa Scale (NOS) will be used for the quality assessment of studies. Findings from this study will recognize the association between PCBs exposure and the risk of endometriosis. Results may provide a new window for identifying the role of PCBs as environmental risk factors in relation to the development of endometriosis.

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**Keywords:** Endocrine disruptors, endometriosis, polychlorinated biphenyls, systematic review.

### Introduction

Endometriosis is a gynecological disease that is known by the existence of endometrial glands and stroma outside the uterine cavity.<sup>[1-3]</sup> Endometriosis impresses 8-10% of women of reproductive age.<sup>[2,4]</sup> It is estimated that 30-50% of women undergoing laparoscopic investigation for infertility have endometriosis.<sup>[5]</sup> The frequency of endometriosis was reported at 29% among Iranian infertile women.<sup>[6]</sup> Its symptoms are including chronic pelvic pain, dyspareunia, dysmenorrhea, and sometimes infertility.<sup>[7]</sup> Although the exact pathophysiology of endometriosis is still unknown, Sampson's theory is one of the strongest accepted theories. Recently, evidence has shown that endometriosis is a multifactorial disease.<sup>[8]</sup>

Several risk factors such as genetic and environmental factors have been suggested

to play important roles in endometriosis etiology. The increasing prevalence of endometriosis calls for a better understanding of the impact of environmental and occupational pollutants.<sup>[1,9]</sup> Polychlorinated biphenyls (PCBs) are one of the types of environmental pollutants that were extensively used in closed applications like heat transfer in capacitors and transformers due to their great physicochemical properties such as un-inflammability, viscosity, stability, and electrical insulation.<sup>[10,11]</sup> However, their manufacture has been banned since the 1970s, but old devices containing these materials are still used in the industry.<sup>[12]</sup> The lipophilic properties of PCBs cause their bio-accumulation within food chains. In addition, PCBs are resistant to environmental destruction, therefore they increase in the environment and the body.<sup>[1,13]</sup> These compounds can be bind to estrogen and androgen receptors, and mimic or

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block the activity of hormones and interfere with endocrine pathways.<sup>[14-17]</sup> Contaminated food and water are the primary sources of PCBs exposure. In addition to the accumulation within the food chain, these toxicants can be moved by weather patterns and influence a great human population at long distances from the origin of their production. Given the toxicity of PCBs to endocrine and immune systems, PCBs may have been linked to the development of reproductive disorders especially endometriosis.<sup>[17]</sup> Evidence reported that Iranian population has relatively low levels of PCBs.<sup>[18,19]</sup> However, there are no studies available in the literature to investigate the relationship between PCBs levels and endometriosis in Iran. Several studies have been conducted in the association between PCBs exposure and risk of endometriosis and evaluated the concentration of PCBs in serum, blood, and peritoneal fluid.<sup>[8,15]</sup> Several studies that most of them had conventional case-control design, showed that higher levels of PCBs in serum was significantly associated with an increased risk of endometriosis (odds ratio [OR]: 4; 95% CI: 1.3-13<sup>[9]</sup> and [OR]: 3.2; 95% CI: 1.0-9.9<sup>[20]</sup>); however, in most of these studies, dose-response has not been reported.<sup>[9,20]</sup>

Some other studies showed that PCBs exposure did not contribute to endometriosis risk ([OR]: 1.3; 95% CI: 0.8-2.2<sup>[21]</sup> and [OR]: 1.02; 95% CI: 0.95, 1.08<sup>[14]</sup>). In a cohort study, researchers revealed that women with serum 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD) concentration of 100 ppt or higher had a nonsignificant risk for endometriosis; however, a dose-response association was unclear.<sup>[22]</sup> Tsukino *et al.*,<sup>[23]</sup> indicated that the OR of endometriosis risk in the highest quartile of total PCBs compared with the lowest quartile was 0.41 (95% CI: 0.14-1.27). We detected two meta-analyses associated with our review. A systematic review and meta-analysis published in 2015 has studied extensively the relationship between environmental chemicals and endocrine disrupting chemicals (EDCs), including PCBs, dichloro-diphenyl-dichloroethylene (DDE), and phthalates with the risk of endometriosis. This systematic review and meta-analysis were carried out on articles that have been published from January 1970 to May 1<sup>st</sup>, 2015 and, the search was performed in PubMed and Ovid Embase classic. Eight studies with 1388 samples (control and endometriosis case) were included in this systematic review and meta-analysis which the cases were confirmed with laparoscopy surgery, general surgery or magnetic resonance imaging (MRI). The results of this systematic review and meta-analysis proved that total PCBs is significantly associated with the risk of endometriosis, ([OR]:2.06; 95% CI: 1.30 to 3.26).<sup>[24]</sup>

A meta-analysis (without comprehensive systematic review) published in 2015 has evaluated the association between exposure to environmental chemicals, including PCBs, bisphenols, and phthalate and the risk of breast cancer and endometriosis. This meta-analysis was performed on articles

that included data from 2000 to 2015. This meta-analysis carried out a PubMed search to identify studies. Six studies with 1350 samples were included in this meta-analysis that cases were confirmed with a laparoscopic examination and/or biopsy. They reported that PCBs exposure is correlated with endometriosis development ([OR]:1.91; 95% CI: 1.05-5.54).<sup>[25]</sup> In our study, we will perform electronic searches in different search engines (five databases) and we will extend the search time interval (from 2000 to the end of 2020) in comparison with the previous studies. This protocol will lead to a systematic review to answer this question, whether PCBs exposure is associated with the risk of endometriosis.

## Objectives

**Primary objective:** Estimating the relation between PCBs exposure and endometriosis risk.

**Secondary objectives:**

1. Estimating the crude and age-adjusted risk of endometriosis in association with PCBs exposure.
2. Assessing heterogeneity of the relation effect size (RR/OR) and finding the potential sources of the heterogeneity (the study designs, methodological quality ...).

## Methods

This protocol was written in accordance with the PRISMA-P guidelines for systematic reviews. The study protocol was approved by Institutional Review Board at Babol University of Medical Sciences (No. IR.MUBABOL.HRI.REC.1398.050).

### Inclusion and exclusion (eligibility) criteria

#### *Type of studies*

We will select all the studies which defined PCBs exposure and endometriosis risk. All retrospective and prospective observational studies including cross-sectional design, traditional case-control design, prospective case-control designs (case-cohort/nested case-control studies) and different cohort design will be included in our systematic review and meta-analysis. The case report, case series studies, *in vitro* studies, animal, and review studies will be excluded.

#### *Type of participants*

The participants of the selected studies will be endometriosis patients (various stages of endometriosis I, II, III, IV) with age 18-49 years which the diagnosis of endometriosis was confirmed by laparoscopy (based on pathology report).

#### *Exposure/Risk factor*

The exposure/risk factor is analysed by gas chromatography (GC) or gas chromatography-mass spectrometry (GC-MS). Therefore, we will select all primary studies which used these methods for PCBs

measurement in blood and serum. All observational studies without GC or GC-MS method will be excluded.

### Outcome

Endometriosis (diagnosed by laparoscopy) associated with PCBs exposure.

### Search strategy and information sources

We will perform electronic or manual searches on Web of Science (WoS/ISI), PubMed/MEDLINE, Scopus, Google Scholar, Embase, the key journals, conferences/congress research papers (as Gray literature), and the reference list of the included primary studies. The search time interval will be from 2000 to the end of 2020. We will not exert the English language restriction. The complete search syntax will be developed based on the medical subject headings (MeSH) database, Emtree database, and free text methods. The main search terms are “endometriosis” and “Polychlorinated biphenyls”.

The generic syntax in the Scopus database is:

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((TITLE-ABS (Biphenyls) AND TITLE-ABS (Polychlorinated)) OR TITLE-ABS(“Polychlorobiphenyl Compounds”) OR (TITLE-ABS (Compounds) AND TITLE-ABS (Polychlorobiphenyl)) OR TITLE-ABS (PCBs) OR TITLE-ABS(“Polychlorinated Biphenyls”) OR TITLE-ABS(“clophen c”) OR TITLE-ABS (PCB) OR TITLE-ABS (phenoclor) OR TITLE-ABS(“polychlorinated biphenyl mixture”) OR TITLE-ABS(“polychlorinated diphenyl”) OR TITLE-ABS (polychlorobiphenyl) OR TITLE-ABS (polychlorodiphenyl) OR TITLE-ABS (Dioxin) OR ALL (Dioxins) OR (ALL (Hydrocarbons) AND ALL (Chlorinated)) OR ALL(“Organochlorine Compounds”) OR (ALL (Compounds) AND ALL (Organochlorine)) OR ALL(“Chlorinated Hydrocarbons”) OR (ALL(“Chlorine Compounds”) AND ALL (Organic)) OR (ALL (Compounds) AND ALL(“Organic Chlorine”)) OR ALL(“Organic Chlorine Compounds”) OR ALL(“Chlorine Compound”) OR ALL(“Chlorine Compounds”) OR (ALL (Compounds) AND ALL (Chlorine)) OR (ALL(“Chlorine Compounds”) AND ALL (Inorganic)) OR (ALL (Compounds) AND ALL(“Inorganic Chlorine”)) OR ALL(“Inorganic Chlorine Compounds”) OR ALL(“Endocrine disrupter”))
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AND

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(TITLE-ABS (Endometrioses) OR TITLE-ABS (Endometrioma) OR TITLE-ABS (Endometriomas) OR ALL (Endometriosis))
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AND

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(PUBYEAR > 2000 AND PUBYEAR < 2021)
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### Study selection

We will conduct the search in the five databases by two independent reviewers according to eligibility criteria and

the duplicated papers will be deleted. The screening phase will be performed and disagreement will be resolved by the opinion of the third expert reviewer.

### Risk of bias assessment

Two investigators will independently assess the risk of bias for each included study. Discordance will be judged by opinion with a third investigator. For study quality assessment, modified Newcastle-Ottawa Scale (NOS) will be used for cohort, case-control, and cross-sectional studies.

### Data extraction

Two independent investigators will assess titles and abstracts to identify potential studies for the review and compared under the direction of a third co-author for quality assurance and to resolve any disagreements. Full text articles of studies that meet the study selection criteria will be reviewed for eligibility for the systematic review and meta-analysis. A standard data extraction form will be used, which will include details of the study design, study setting, study population, demographic and baseline characteristics, sample sizes, methodology, exposure, effect measurement, control conditions, and outcome measurement.

### Strategy for data synthesis and heterogeneity assessment

For quantitative data, where possible, the concordant relative risk measure (any of OR, RR, or IRR) or standardized mean differences (SMD) and their 95% confidence intervals will be calculated from the data generated by each included study. The combination method will be either the fixed effect model (FEM) or the random effects model (REM), according to the methodological similarities between included studies. A forest plot will be plotted by the combined effect size. Heterogeneity between combined studies will be tested using standard  $X^2$  test (Cochran's  $Q$  test) of homogeneity (significant for  $P < 0.1$ ) and I-square measure. The  $I^2$  measure equal to or more than 50% will be assumed as severe heterogeneity. Where statistical pooling is not possible, sub-group analysis or meta-regression method will be performed for finding the heterogeneity determinant(s). Funnel plots, followed by Begg's and Egger's plot and test, will be done to analyse the publication bias. The trim and fill method will be performed when the results of Begg's or Egger's tests show publication bias which cannot be overlooked ( $p$  value  $< 0.10$ ). The one-out remove method will be used to assess sensitivity analysis. In this regard, all studies will be combined without one study. If one or more combined measures will be different from the others, the study characteristic(s) should be evaluated. Although the final plan is a meta-analysis, it will be possible only when we see what data is extracted and made available from the systematic review.

### Discussion

There is increasing evidence suggesting the association between exposure to persistent chlorinated and brominated environmental



pollutants and endometriosis over the last decade.<sup>[8,9]</sup> In animal model studies, consistent associations have been previously demonstrated between exposure to these components and the onset of endometriosis.<sup>[26]</sup> Despite previous researches, existing studies remain relatively inconclusive due to methodological and population heterogeneity. Two meta-analyses associated with our review have extensively studied environmental chemicals, while we will focus on PCBs. Two previous meta-analyses performed electronic searches in limited search engines including PubMed and Ovid Embase, while we will carry out electronic searches in extensive search engines. Moreover, the search time interval in our study will be from 2000 to the end of 2020. This paper is a protocol study on systematic review of the relationship between human exposure to PCBs and the risk of endometriosis. The result of this study can lead to a systematic review to identify the role of PCBs as environmental risk factors in association with the risk of endometriosis.

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### Conflicts of interest

There are no conflicts of interest.

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