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REVIEW

Cadmium Associated Preeclampsia: A Systematic Literature Review of Pregnancy and Birth Outcomes

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Abstract

Preeclampsia (PE), caused by multiple factors, is one of the most serious complications of pregnancy. Cadmium (Cd) is a heavy metal environmental pollutant, reproductive toxicant, and endocrine disruptor, which can increase the risk of PE. Cd toxicity due to occupational, diet, and environmental factors has worsened the risk. Studies showed elevated Cd concentration in maternal blood and placenta of PE women. However, the implicit association between Cd associated PE is still not highlighted. We systematically reviewed Cd-associated PE and its effect on pregnancy and birth outcomes. Based on "Preferred reporting items for systematic reviews and meta-analyses (PRISMA)" guidelines, eighty-six studies were identified by PubMed, Web of Science (WOS), and Scopus databases. Publications were included until October 2023 and articles screened based on our inclusion criteria. Our study identified that the exposure of controlled and uncontrolled Cd induces PE, which negatively affects pregnancy and birth outcomes. Given the serious nature of this finding, Cd is a potential adverse agent that impacts pregnancy and future neonatal health. Further comprehensive studies covering the whole trimesters of pregnancy and neonatal developments are warranted. Data on the molecular mechanisms behind Cd-induced PE is also essential for potential preventive, diagnostic, or therapeutic targets.

Keywords Preeclampsia · Cadmium · Pregnancy · Maternal · Prenatal · Birth outcomes

Introduction

Preeclampsia (PE) is one of the leading causes of preterm birth, direct maternal morbidity, and mortality [1], affecting 8 to 10% of pregnancies around the world [2]. This overwhelming percentage of preeclamptic pregnancies has significantly increased the burden on the economy, clinicians, and healthcare systems [3, 4]. There exist disparities in preeclampsia outcomes between low- and high-income countries. These differences can be attributed to various factors, including inadequate knowledge [5], financial constraints, laboratory result delays, insufficient medical supplies and equipment, psychosocial stress, societal beliefs, inadequate patient counseling, and healthcare resources [6, 7]. Meanwhile, the inducer of PE is multifactorial and may include nutritional, immunological, environmental, or genetic factors [8, 9].

Focusing on environmental element, cadmium (Cd) is a non-essential heavy metal with primary exposure potentially that comes from food such as shellfish, rice, and leafy vegetables. It is also among the abundant compounds found in cigarette smoke. It accumulates in the liver, kidney, and bones [10], making urine Cd representative of Cd accumulation in the renal cortex.

Cadmium is also identified as an endocrine and reproductive system disruptor with an effect on the synthesis and regulation of hormones, as well as vascular functions [11, 12]. Cd contributes to immune regulation related to pregnancy-specific hypertension and is associated with PE.

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Placental Cd was recorded elevated in PE women, although the association and the mechanism behind this are still poorly understood [13].

Cadmium has a long biological half-life (up to 38 years for the human kidney and 19 years for the human liver) [14]. The common route of exposure is via inhalation (approximately 25%) and oral (5%) [15]. Both inhalational and oral Cd absorption increase during pregnancy [16] due to increased respiratory rate, decreased gastrointestinal motility, or decreased gastric emptying [17]. Overexpression of gut receptors and transporters due to high nutrient demand [18] may also promote Cd absorption. Cd accumulates in the lung and gut before being distributed to the liver, kidneys, placenta, mammary glands, uterus, and fetus [19, 20] and can be excreted into the milk [21, 22]. The presence of Cd in breast milk was detected [23, 24] and transferred to mouse pups via lactation [25]. The intestinal absorption of Cd is facilitated by various transporters, such as the divalent metal transporter-1 (DMT-1), calcium channels, amino acid transporters, and via endocytosis of the cadmium-metallothionein (CdMT) complex [26, 27].

Pregnancy outcomes are negatively impacted by PE [28, 29]. Among the consequences on the offspring from pregnancies complicated with PE include perinatal, neonatal, or infant morbidity/mortality [30]. Often, the only means to halt the progression of PE is preterm delivery of the fetus. The serious outcomes of preterm birth include respiratory complications, intravascular hemorrhage, necrotizing enterocolitis, and retinopathy of prematurity [31]. PE also causes thrombosis towards the placenta vasculature, leading to poor blood supply which subsequently affects the fetal growth potential [30].

A multifaceted approach to the management and therapy of preeclampsia is imperative [32, 33]. Screening for hypertensive disorders in the third trimester using a combination of maternal factors and angiogenic markers significantly improves prediction accuracy compared to biomarkers alone [32]. This indicates the importance of integrating comprehensive maternal health profiles in screening protocols to identify women at high risk earlier and more reliably. New advanced biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) could enhance early detection and intervention strategies [33].

To date, existing systematic literature reviews focused on the effects and management of PE and pregnancy and did not specifically highlight the impact of Cd-induced PE. This review aimed at evaluating the existing literature of Cd-induced PE and its effect on pregnancy and birth outcomes. Our review will provide vital information for the adverse impact of maternal Cd in escalating PE through maternal and fetal parameter alterations.

Methods

The research question (RQ) of this study is based on the PICO framework. The aspects are detailed below:

- Patient/population: pregnant rats and women (JEG-3 cells)
- Intervention/indicator: Cd-associated PE pregnancy
- Comparison: pregnancy and birth outcomes
- Outcomes: adverse effects of Cd exposure on maternal and fetal parameters
- Research question: what are the adverse effects of Cd-associated PE on pregnancy and birth outcomes in terms of maternal and fetal parameters alteration?

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [34] was employed for this systematic review. PubMed, Web of Science (WOS), and SCOPUS were the search tools used to identify studies focusing on the effects of Cd-induced PE on pregnancy and birth outcomes. The keywords (combinations are presented in Appendix) used for mining the databases were "cadmium," "preeclampsia," "pregnancy," "birth," "prenatal," and "maternal." Initially, the studies were searched without language restriction, type of study (original research, review article, case report, etc.), and full-text availability. The studies published from inception until October 2023 were searched from the databases and included following the inclusion criteria. The original research articles focusing on the effect of Cd-induced PE during pregnancy in human and animal models were included, whereas review articles, case reports, editorials, studies lacking Cd exposure during pregnancy, or studies lacking Cd-induced PE during pregnancy were excluded. For studies with more than one publication from the same sample, the publication with the largest data or the latest publication was considered.

The study quality was evaluated by assessing risk of bias in each study using Cochrane review criteria [35]. The authors FS and RS evaluated each study separately. Based on seven domains (mentioned in Fig. 2), the studies were categorized into "low risk," "unclear," and "high risk." The categories made by FS and RS were discussed with other authors (YSK, FR, and NAMK) to resolve classification discrepancies.

Results

The details of the study selection process are shown in Fig. 1. Out of eighty-six (86) records identified from PubMed, WOS, and SCOPUS databases, only thirteen (13) studies met predefined inclusion/exclusion criteria. The number

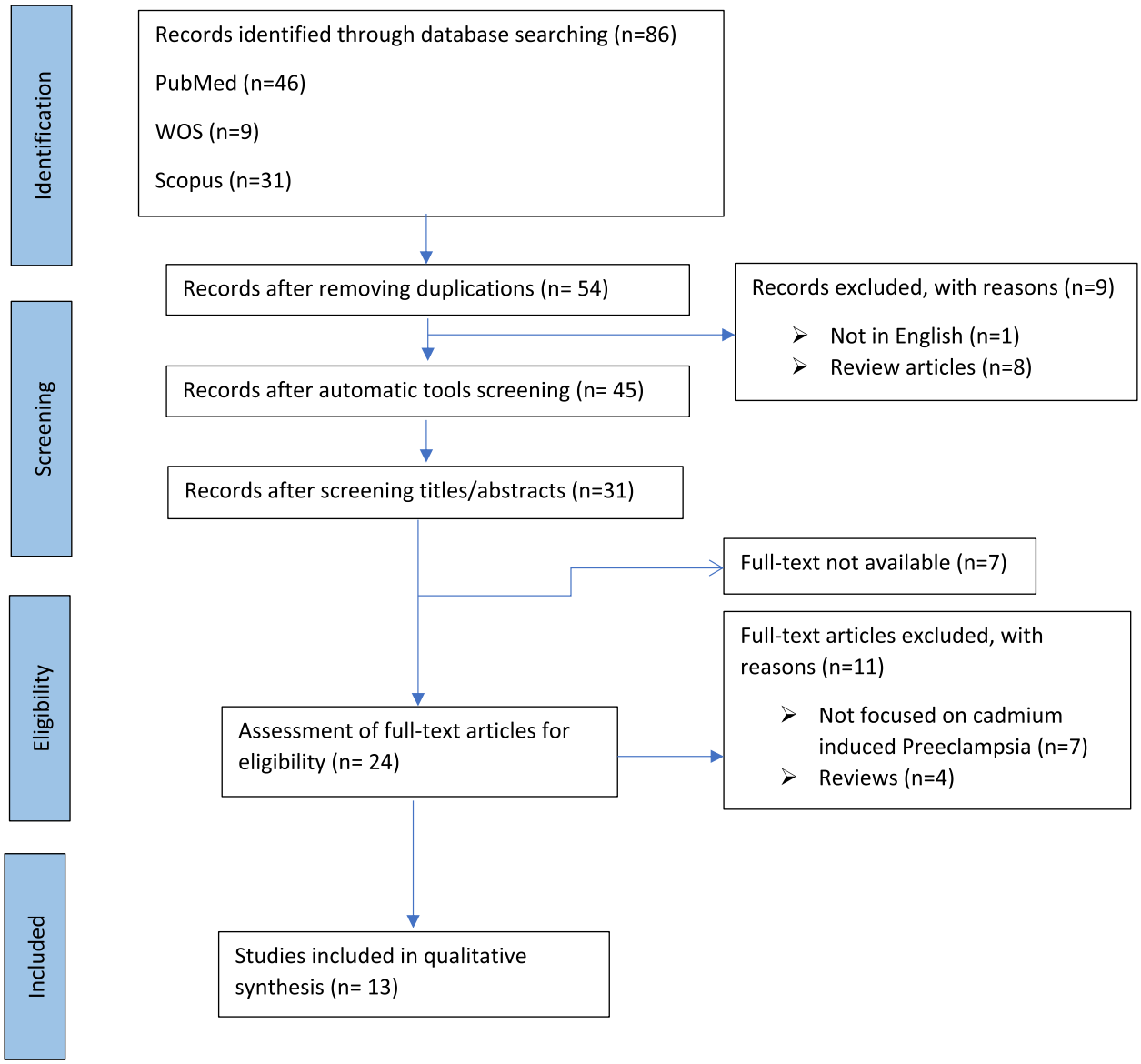

Fig. 1 Article selection process

Table 1 Factor wise classification of the included studies

Factor	Number of studies	References
Cadmium level and preeclamptic conditions	9	[28, 29, 36–42]
Endothelial dysfunction	3	[36, 38, 40, 43]
Oxidative stress	3	[37, 41, 44]
Placental growth	6	[28, 41, 43–46]
Antiangiogenic	3	[28, 38, 39]
Maternal body weight	6	[37, 38, 40, 41, 43, 46]
Urinary protein	2	[38, 46]
Blood pressure	4	[28, 37, 38, 46]
Fetal growth	4	[29, 38, 41, 43]
Birth weight	4	[28, 29, 37, 41]
Preterm birth and gestational age	4	[28, 29, 37, 44]
Miscarriage	0	---

of studies excluded along with the reasons is detailed in Fig. 1.

Table 1 presents factors discussed by the studies included in this review.

The characteristics and findings of the studies discussing the effects of Cd-induced PE on JEG-3 (clonal human cell line) [47], women, and rats to determine the effects on pregnancy and birth outcomes are summarized in Table 2.

Risk of bias was evaluated in each of the thirteen included studies (Fig. 2). Six studies [28, 29, 36, 37, 39, 45] involving women and JEG-3 cells were unclear in terms of randomized sequence generation, while seven others published on rats/rodents model stated the method. None of the studies clearly mentioned allocation concealment. Studies on women [29, 37, 42] involved blinding of the study personnel, although it was unclear for the remaining 10 studies. All studies were categorized as "low risk" in the remaining four biases (detection, attrition, reporting, other).

Assessment of multiple systematic reviews (AMSTAR 2) was employed to further categorize the studies as poor, moderate, or good. Based on assessment criteria of type of study, publication status, effectiveness of methodology, quality of conclusions, risk of bias, and category of findings pool, all included studies were regarded as of high quality.

Discussion

The results presented in Table 2 highlight Cd as an inducer of preeclampsia and its effects on pregnancy and birth outcomes. Detailed discussion on the effects of Cd-induced PE in the light of existing literature on hypertension, proteinuria, maternal weight, endothelial dysfunction, placental growth and antiangiogenic factors, oxidative stress, fetal growth, spontaneous abortion/miscarriage, preterm birth and gestational age, and birth weight is presented in the following sections.

Preeclampsia: Cadmium as an Inducer

Evidence of contaminant Cd exposure is emerging [49, 50]. Cd is a known heavy metal, toxicant, and endocrine disruptor involved in the regulation of several hormones [11, 12]. It enters the systems through inhalation, ingestion, or dermal contact [29]. Contaminated food (plant-derived, rice), water, and tobacco are the major sources of Cd exposure [51]. Cadmium concentration level is associated with PE. High maternal blood and placental Cd levels were reported in PE patients [28] with a 1.15 times higher risk of PE for each standard deviation increase in Cd level [37].

By geographical locations, Cd concentrations were reported higher in Asian than Swedish or South African women. On clinical data, the incidence of PE shows wide variation between regions and is highest among developing countries [52, 53]. In developed countries, dietary Cd intake has decreased due to stricter environmental controls, although it has increased in some developing countries [11]. For instance, the average Cd intake in 2016–2019 in China was 17.3 lg/day, a 47% decrease over 2009–2013 [13]. On the other hand, in Vietnam, rice consumption caused the highest exposure to Cd, while metal recycling communities consumed higher amounts of Cd in their diets [15].

Dietary intake of Cd, use of consumer goods (electric batteries, paints, etc.), industrial wastes, soil fertilizers, and tobacco smoke were reported as the sources of Cd [54]. High blood Cd in preeclamptic women and animal models following Cd exposure were documented [12, 55].

Information about the molecular mechanisms behind Cd-induced PE is essential not just for detection but also for effective PE control. Brooks et al. [39] demonstrated that Cd-induced PE led to miRNA dysregulation. Furthermore, the changes in miRNA expression were robust in relation to Cd level in the preeclamptic group compared to the normotensive group. Hence, the role of miRNAs in predicting the regulation of angiogenesis-associated transforming growth factor-beta (TGF-β) pathway will be an area of future targets for PE treatment.

Hypertension

Cd exposure leads to hypertension [56, 57]. There exists a possibility of dysfunction and damage of the renal tubule due to Cd exposure and high blood pressure [58]. The association between blood pressure and blood Cd level is positive, and Cd level was significantly higher among Korean hypertension subjects [56]. Aramjoo et al. [59] conducted a systematic review and documented a positive relationship between hypertension and hair Cd levels. The relationship between urinary Cd and blood pressure was also positive [60].

Experimental evidence has also suggested an association between Cd and cardiovascular diseases [61]. In animal model of Cd induction, increased systolic blood pressure in pregnant rats was evident [38, 46].

Proteinuria

Proteinuria, an elevated protein level in urine, is another feature of PE [40]. Cd exposure induces renal and proximal tubules damage, resulting in urinary abnormalities, including filtered urinary protein [38, 62]. Furthermore, increased urinary albumin was also evident in pregnant rats following Cd administration [46]. Renal intoxication and nephrotoxicity induced by Cd were reported due to the activation of inflammatory responses [63].

Table 2 Details of the studies evaluating the effects of Cd-induced PE on pregnancy and birth outcomes

Author	Subject	Dose, exposure, and procedure	Outcomes, effects, and measurement techniques	Key findings
Paniagua et al. [36]	Human choriocarcinoma cell line JEG-3	a) 0.6, 1.2, and 2.5 µM $CdCl_2$ for 0, 1, 3, 6 and 24 h b) The exposure began following 2 h of cell starvation in 0.5% FBS/DMEM. Interleukin-6 (IL-6) post-Cd exposure was quantified using ELISA FBS: fetal bovine serum DMEM: Dulbecco's modified eagle's medium	a) CytoTox 96® NonRadioactive b) Cytotoxicity Assay: Lactate dehydrogenase c) Lactate dehydrogenase (LDH) leakage to analyze cytotoxic effect of $CdCl_2$, PD 98059 (Erk inhibitor), and SP600125 (JNK inhibitor) d) Spectrophotometry (at 490 nm): LDH activity in cell supernatants	a) Cd accumulated in the liver, kidney, and placenta during pregnancy b) Interleukin IL-6 is linked to PE and played a role in maternal endothelial dysfunction
Li et al. [28]	Women (JEG-3 cells collected immediately after delivery)	a) JEG3 cells exposed to 20 µM $CdCl_2$ at different time points, and Dio2 inhibitor, 100 µM IOP b) Cells were treated with 100 µM IOP for 24 h to find the effect of thyroid hormone receptor signaling on the angiogenic factor DIO2: Deiodinase 2 IOP: Iopanoic acid	a) Maternal blood and placental Cd were measured by inductively coupled plasma mass spectrometry (ICP-MS), Perkin Elmer NexION 350X) b) Placental angiogenesis detected by immunohistochemistry using CD34	a) The exposure of Cd: i) Thyroid hormone receptor α and Dio2 expressions were down-regulated ii) Thyroid hormone receptor β was unaffected iii) PLGF and VEGF expressions decreased, while sFlt1 increased b) The disturbance in thyroid hormone receptor signaling caused decreased placental angiogenesis. This was associated with PE c) PE compared to control groups: i) High maternal blood and placental Cd concentration at birth ii) Reduced infant birth and placental weights
Liu et al. [37]	1274 women (Boston Birth Cohort)	Measured trace minerals, heavy metal, and mercury from red blood cells collected within 24–72 h of delivery	a) Lower birth weight and shorter gestational period b) Increased risk of PE by 15% with 1 standard deviation increased in Cd	Higher blood Cd concentration increased the chances of PE
Wang et al. [29]	132 women (51 preeclamptic, 51 normal pregnant, and 30 normal women without pregnancy)	a) Blood samples: 28th to 40th weeks of pregnancy b) Placental tissue samples: within 10 min of delivery	Cd measured by ICP-MS	Higher Cd level increased the risk of PE, lower birth weight, and caused fetal growth restrictions
Brooks and Fry [45]	JEG3 cells	0.028, 1, 10, and 25 mM $CdCl_2$	Association between placental cell migration and Cd concentration	a) Cd exposure decreased placental trophoblast cell migration b) Activated TGF-b signaling pathway decreased cell migration c) miRNAs were critical for TGF-b
Brooks et al. [39]	JEG-3 cells (translational study) (16 preeclamptic and 16 healthy women)	Placental tissues of 32 women	Gene expression analysis using genome-wide microarray	Cd caused dysregulation of miRNA which is a feature of PE
Laine et al. [42]	a) 172 women (86 preeclamptic and 86 healthy) b) Control Study	Biopsies of the central zone of placenta	Associations between metals and PE	Essential metals may reduce the odds of Cd-induced PE

Table 2 (continued)

Author	Subject	Dose, exposure, and procedure	Outcomes, effects, and measurement techniques	Key findings
Eisenmann and Miller [44]	Rodents and women placentas (Placental explants of women with pre-existing conditions were not used)	Placental tissues exposed to $CdCl_2$ at 0, 0.2, 2, 20, 40, or 100 µM, for two 12 h periods	The effect of Cd on: a) human placental production of thromboxane A b) prostacyclin c) human term placenta in vitro induces changes in the production of TxB and 6-keto-PGF1α, which would be conducive to vasoconstriction and blood coagulation	a) High placental Cd affected thromboxane A/prostacyclin ratio by affecting the production of 6-keto-PGF1α b) Low Cd concentration (up to 100 PM) causes no significant effect on TxB production. Lactate production was reduced at 100 FM, without affecting human chorionic gonadotropin (hCG) production and release
Zhang et al. [38]	a) Wistar rats b) Enrolled patients	a) Conditions: 23 °C with 12:12 light: dark cycle b) Exposure: 0.125 mg/kg Cd from days 9 to 12 of pregnancy	a) Maternal blood collected through cardiac puncture on Day 21 of pregnancy b) Induced cytosine deaminase in B cells, Cd, and progesterone $_{levels}$ were recorded in preeclamptic patients	a) Higher Cd and lower progesterone levels in preeclamptic women in comparison to healthy pregnancy b) Immune abnormalities induced by Cd contributed to PE
Zhang et al. [40]	a) Wistar rats b) Patients at 28–40 weeks of pregnancy	0.125 mg/kg $CdCl_2$ (i.p.) from days 9 to 14 of pregnancy, (23 °C, 12:12 light: dark cycle)	Effect of Cd on immunoglobulin production	a) Higher blood Cd levels in preeclamptic patients b) Cd-induced PE caused hypertension, proteinuria, immune abnormalities, and small fetal size
Shen et al. [43]	Pregnant rats	0.125 mg/kg/d $CdCl_2$	a) SCH58261 (antagonist of receptor) was used to measure the role of adenosine A2A receptor (A2AR) in Cd-induced PE b) A2AR expression was measured in PE and normal pregnant women	a) Pathological progression of Cd-induced PE was mediated by Placental A2AR b) A2AR inhibits PE development due to the increased sirtuin-1 (sirt1) and decreased hypoxia-inducible factor-1α (HIF-1a)
Zhang et al. [41]	Rats	0, 0.25, and 0.5 mg/kg b.w./day $CdCl_2$ (i.p.) from days 14 to 19 of pregnancy	a) Kidney and placental tissue morphology by means of hematoxylin and eosin (H&E) staining b) ICP-MS is used to detect blood Cd	a) Preeclamptic conditions induced by the increased oxidative DNA damage b) Phenotypic characteristics of human PE (hypertension, proteinuria) developed in Cd-exposed pregnant rats
Wang et al. [46]	Female Sprague–Dawley rats (10 to 12 weeks old)	a) 0, 0.25, and 0.5 mg/kg bw/day $CdCl_2$ (i.p.) from days 5 to 19 of pregnancy b) Urine collection on days 3 and 19 of pregnancy	a) Toxic effects of Cd during pregnancy and endocrine intervention were investigated b) Serum and placental corticosterone measured using ELISA c) Cd measured in maternal, placental, and fetal blood using ICP-MS	a) Cd altered placental glucocorticoid, leading to PE b) Cd exposure caused hypertension, endotheliosis, placental abnormalities, proteinuria, glomerular abnormalities, and small fetal size

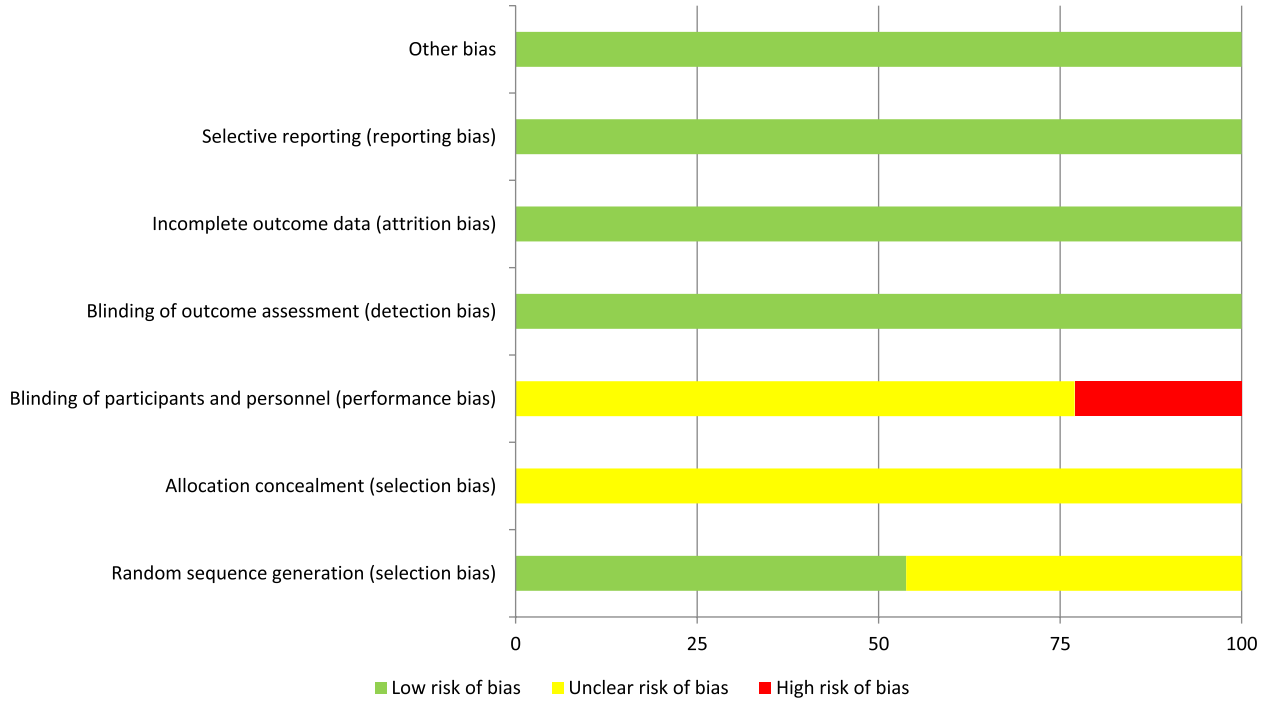

Fig. 2 Assessment result for the risk of bias

Maternal Weight

Preeclampsia due to Cd exposure was reported to reduce maternal and fetal weights [38, 40, 43, 64]. However, inconsistency occurs as the effect of Cd on maternal body mass index (BMI) was reported high in another study [37].

Endothelial Dysfunction

The mechanism of endothelial dysfunction behind Cd exposure is closely related to oxidative stress (OS) [65]. The deposition of Cd on endothelium signifies abnormal lipid metabolism and endothelial dysfunction [66]. Cd accelerates triglyceride decomposition and accumulation of free fatty acids, leading to cell death and endothelial dysfunction due to cytotoxicity and induced abundance of reactive oxygen species [48].

On the other hand, preeclampsia is also associated with early and late pro-inflammatory states which contributes to maternal endothelial dysfunction [67], also with OS as the principal mechanism [48, 65]. Increased contraction of capillary vessels, endothelial swelling, and hyperplasia [43] reduced capillary space and thickened renal walls [38, 40], ultimately leading to endothelial dysfunction [38, 40, 43].

Placental Growth and Antiangiogenic Factors

Cadmium-induced PE poses risks for placental growth [68]. Cd placental accumulation reduces membrane protein expression, leading to poor placental transport [69]. Increased lipid hydro-peroxides and activation of lipid peroxidation were previously proposed as the mechanism to explain placental Cd accumulation [44].

Increased placental and maternal blood Cd in preeclamptic women decreased angiogenesis by down-regulating thyroid hormone receptor signaling [28]. Environmental Cd exposure causes GCN-2-mediated mitochondrial stress leading to poor placental angiogenesis and fetal growth [70]. On the other hand, gestational Cd exposure impairs placental angiogenesis via downregulating vascular endothelial growth factor A (VEGF-A) and dysregulation in the hormone receptor signaling pathway [71]. On the other hand, decreased CD34 staining in the placenta was consistent with anti-angiogenesis in the Cd-treated rats, with poor placentation caused by angiogenic factors and aberrant growth signaling was postulated to be the casual reason [39].

The decidual natural killer (dNK) cells secrete VEGF and placental growth factor (PGF), as well as cytokine interferon-γ (IFN-γ) [30]. VEGF and PGF promote angiogenesis beginning during the early pregnancy, while dNK cell-derived IFN-γ modify and promote vasodilation of decidual spiral arteries. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1), a tyrosine kinase protein with antiangiogenic properties, in the placenta of PE women diminished the circulating free VEGF and placental growth factor (PLGF), promotes endothelial dysfunction

in vitro, and induces hypertension, proteinuria, and also glomerular endotheliosis [28]. In addition, dysregulation in the hormone receptor signaling [71] and decreased maternal circulating CD34 were also correlated with PE [38, 39].

Oxidative Stress (OS)

Cadmium-induced PE causes overabundance of reactive oxygen species leading to oxidative toxicity [73]. The effects of Cd-induced OS on DNA [41, 74], molecular metabolism, and immune responses were reported previously [37, 75]. When naturally produced free radicals in humans may pose a positive impact on the immune system, their negative effects on proteins, lipids, and DNA oxidation have been largely illustrated [72, 76]. Normally functioned cellular machinery will ensure non-pathological embryonic as well as placental growth.

Fetal Growth

Fetal growth is a useful marker for *in utero* fetal well-being. PE and fetal growth restriction (FGR) occur in 3 to 5% of pregnancies. It has been reported that Cd-induced PE restricts fetal growth [68, 70, 77] causing decreased birth weight [78] and head-tail length [38, 43] in a dose-dependent manner [29, 41]. The prevalence of PE (caused due to hypertensive disorders of pregnancy) is up to 15% in the developing countries with a mortality rate of 5–15%, leading to a risk factor for the health of fetal due to preterm birth [78].

Spontaneous Abortion/ Miscarriage

Placental accumulation of Cd leads to PE, growth restrictions, and miscarriage [42, 79, 80]. However, none of the studies included in this systematic review focused on miscarriage. This could be probably due to the criteria set in this study, which was dependent on the development of hypertension 20 weeks into pregnancy and the major focus being after viable pregnancy (more than 22 weeks). However, to the best of our knowledge, the complications pertaining to those 2-week intervals (between 20 and 22 weeks) have not been described in literature.

Hence, this study highlights the need for a comprehensive study to provide data on spontaneous abortion following PE diagnosis. It is also essential to establish how Cd exposure affects early fetal and post-natal development.

Preterm Birth and Gestational Age

Preterm birth is one of the leading causes of prenatal mortality and morbidity [81, 82]. Cd exposure might be associated with preterm birth [61] and originates from maternal pathophysiology [83].

Placental dysfunction in preeclamptic women of reproductive age poses a higher risk of preterm birth, lower mean birth weight percentile, and shorter gestational age [84]. The risk is higher among preeclamptic women with age less than 25 years [85]. The pathology behind gestational age, low birth weight, and PE is similar in exposure to toxicities [2]. However, in contrast, the role of Cd (induced by smoking) in causing placental abruption [44] and preterm birth [29] was insignificant as opposed to other reports [28, 37].

Birth Weight (BW)

Low BW is defined as birth weight less than 2500 g [86]. It is associated with increased neonatal and infant mortality [87]. Elevated maternal blood Cd has been associated with decreased fetal BW [29, 88, 89] and influences postnatal survival [90]. Accumulation of reactive oxygen and dysfunction of placental mitochondria resulting from Cd exposure were thought to be among the mechanisms [91]. In addition, low placental and fetal BW in preeclamptic women may also be associated with shorter gestational age [28, 29, 37, 41].

Strength and Limitations

The study has summarized the effects of PE induced by the environmental pollutant Cd on pregnancy and birth outcomes, providing useful insights for clinicians and the overall healthcare system. Another strength is the holistic review of the search question by including studies published until October 2023.

The use of terminologies/synonyms in keywords such as "gestation" or "pregnancy-induced hypertension" in place for "pregnancy" or "preeclampsia" might affect the search outcomes and number of articles captured by the employed databases. The exclusion of articles in a language other than English may also create bias in the search results.

With regards to the absence of protocol registration, this review was initiated prior to the awareness of the importance of protocol registration; hence, this aspect is unavailable here. However, despite the absence of protocol registration, the established PRISMA guidelines strictly followed here helped maintain the transparency and methodological rigor. The predefined search strategy, inclusion/exclusion criteria, and data extraction process helped ensure a systematic approach. The importance of protocol registration, although not mandatory, is recommended to enhance the credibility and reproducibility of systematic reviews and will be considered in our future reviews.

Conclusion and Recommendations

The findings of this study demonstrated the adverse effects of Cd-induced PE on pregnancy and birth outcomes in both human and animal models. Our review has linked Cd-induced PE to adversities related to the symptoms, altered biochemical markers as well as maternal-fetal changes.

Further works covering all pregnancy trimesters and postnatal development are warranted to acquire definitive results on the sequelae of Cd-induced PE during pregnancy. Data on the molecular mechanisms behind Cd-induced PE is also essential for potential preventive, diagnostic, or therapeutic targets. In addition, biomonitoring of maternal exposure to Cd will help reduce future adverse pregnancy and birth outcomes associated with PE.

Appendix

Keyword combinations used for searching databases

No	Keywords combination
1	"cadmium" AND "preeclampsia" AND "pregnancy"
2	"cadmium" AND "preeclampsia" AND "pregnancy" AND "birth"
3	"cadmium" AND "preeclampsia" AND "pregnancy" AND "prenatal"
4	"cadmium" AND "preeclampsia" AND "pregnancy" AND "maternal"
5	"cadmium" AND "preeclampsia" AND "birth"
6	"cadmium" AND "preeclampsia" AND "birth" AND "prenatal"
7	"cadmium" AND "preeclampsia" AND "birth" AND "maternal"
8	"cadmium" AND "preeclampsia" AND "pregnancy" AND "birth" AND "prenatal"
9	"cadmium" AND "preeclampsia" AND "pregnancy" AND "birth" AND "maternal"
10	"cadmium" AND "preeclampsia" AND "pregnancy" AND "birth" AND "prenatal" AND "maternal"

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Author Contributions The authors FS and RS identified and evaluated each study separately. Based on seven domains (mentioned in Fig. 2), the studies were categorized into "low risk", "unclear", and "high risk" by FS and RS and then checked by YSK, FR, and AAA. The detailed review evaluation of the selected studies was made by FS and RS. The results were discussed with four other authors (YSK, FR, AAA, and NAMK). These four authors checked and verified the findings.

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Data Availability Data sharing does not apply.

Declarations

Competing Interests The authors declare no competing interests.

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