Wiku Andonotopo*, Muhammad Adrianes Bachnas, Julian Dewantiningrum, Mochammad Besari Adi Pramono, Muhammad Ilham Aldika Akbar, Ernawati Darmawan, I. Nyoman Hariyasa Sanjaya, Dudy Aldiansyah, Sri Sulistyowati, Milan Stanojevic and Asim Kurjak

Endocrine disrupting chemicals: translating mechanisms into perinatal risk assessment

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Abstract

Objectives: To evaluate the evidence linking prenatal exposure to environmental endocrine-disrupting chemicals (EDCs) – including bisphenol A (BPA), phthalates, and per- and polyfluoroalkyl substances (PFAS) – with adverse pregnancy and fetal developmental outcomes, and to assess the potential translation of this evidence into clinical perinatal risk assessment.

Methods: A systematic literature search was conducted in PubMed, Scopus, and Web of Science for studies published between January 2000 and May 2025. Eligible studies included epidemiological and experimental research addressing prenatal EDC exposure and fetal-placental outcomes. After duplicate removal and screening, 52 studies met inclusion criteria and were categorized by study type (epidemiological, mechanistic, translational). Data extraction included exposure metrics, critical developmental windows, and reported effect sizes (odds ratios, risk ratios, hazard ratios).

Results: Evidence suggests that EDC exposure during early pregnancy is associated with placental dysfunction, altered fetal growth trajectories, endocrine and epigenetic modifications, and increased risk of selected neonatal outcomes. Effect sizes were variable, often modest (many<2.0), but consistently indicated biological plausibility supported by mechanistic data. Biomonitoring studies demonstrate widespread EDC exposure across populations, including higher body burdens in lower-income and racially diverse groups. Despite robust basic science evidence, clinical screening for EDC exposure remains limited, and routine risk assessment frameworks rarely incorporate environmental chemical exposures.

Conclusions: Prenatal EDC exposure is biologically linked to disrupted fetal-placental development, yet translation into clinical practice remains incomplete. Integrating environmental exposure assessment and preventive counseling into perinatal care may improve maternal-fetal health and reduce disparities.

Keywords: endocrine disruptors; fetal-placental development; environmental exposure; perinatal outcomes; prenatal risk assessment

***Corresponding author: Wiku Andonotopo**, MD, PhD, Department of Obstetrics and Gynecology, Fetomaternal Division, Women Health Center, Eka Hospital, BSD City, Serpong, Tangerang, Banten, Indonesia, E-mail: wiku.andonotopo@gmail.com. https://orcid.org/0000-0001-9062-8501

Muhammad Adrianes Bachnas and Sri Sulistyowati, Department of Obstetrics and Gynecology, Fetomaternal Division, Medical Faculty of Sebelas Maret University, Dr. Moewardi Hospital, Surakarta, Indonesia. https://orcid.org/0000-0002-1710-3909 (M.A. Bachnas)

Julian Dewantiningrum and Mochammad Besari Adi Pramono, Department of Obstetrics and Gynecology, Fetomaternal Division, Medical Faculty of Diponegoro University, Dr. Kariadi Hospital, Semarang, Indonesia

Muhammad Ilham Aldika Akbar and Ernawati Darmawan, Department of Obstetrics and Gynecology, Maternal-Fetal Medicine Division, Faculty of Medicine, Airlangga University, Dr. Soetomo General Hospital, Surabaya, Indonesia

I. Nyoman Hariyasa Sanjaya, Department of Obstetrics and Gynecology, Maternal-Fetal Medicine Division, Faculty of Medicine, Udayana University, Prof. Dr. I.G.N.G Ngoerah General Hospital, Bali, Indonesia

Dudy Aldiansyah, Department of Obstetrics and Gynecology, Fetomaternal Division, Faculty of Medicine, Sumatera Utara University, H. Adam Malik General Hospital, Medan, Sumatera Utara, Indonesia

Milan Stanojevic, Department of Neonatology and Rare Diseases, Medical University of Warsaw, Warsaw, Poland

Asim Kurjak, Department of Obstetrics and Gynecology, Medical School University of Zagreb, Zagreb, Croatia

Introduction

The intrauterine environment is a critical determinant of lifelong health, with the placenta serving as the central mediator of maternal–fetal exchange and endocrine signaling. Increasing attention has focused on environmental endocrine-disrupting chemicals (EDCs) – exogenous substances capable of interfering with hormone pathways and developmental processes [1, 2]. Widespread exposure to compounds such as bisphenol A (BPA), phthalates, and per- and polyfluoroalkyl substances (PFAS) has been documented in pregnant populations worldwide, raising concerns about

their potential contribution to adverse perinatal outcomes [3–6]. To guide the evidence base for this review, the literature selection process is detailed in Figure 1 (PRISMA 2020 flow diagram). Furthermore, key exposure–outcome associations from epidemiological studies are summarized in Table 1, providing an overview of the strength and consistency of reported findings.

Recognition of EDCs as a global public health issue has grown steadily since the early 2000s. Initial risk assessments highlighted their biological activity even at low-dose exposures and their persistence in environmental and biological matrices [7]. Large-scale biomonitoring programs, including the National Health and Nutrition Examination Survey (NHANES), demonstrated detectable levels of multiple EDCs in nearly all pregnant women assessed [18, 19]. Subsequent analyses revealed that exposure is not confined to industrialized settings but extends across diverse geographic regions and socioeconomic groups (Figure 2) [11, 16, 23, 24].

Mechanistic evidence indicates that EDCs disrupt placental function through multiple pathways, including altered steroidogenesis, impaired nutrient transport, oxidative stress, mitochondrial dysfunction, and inflammatory activation [25–29]. Emerging epigenetic data demonstrate that these compounds can modify DNA methylation, histone acetylation, and microRNA expression in placental and fetal tissues, potentially altering developmental programming across generations [8, 30]. These mechanistic insights are summarized in Figure 3 and Table 2.

Epidemiological studies have linked prenatal EDC exposure with a spectrum of adverse outcomes, including

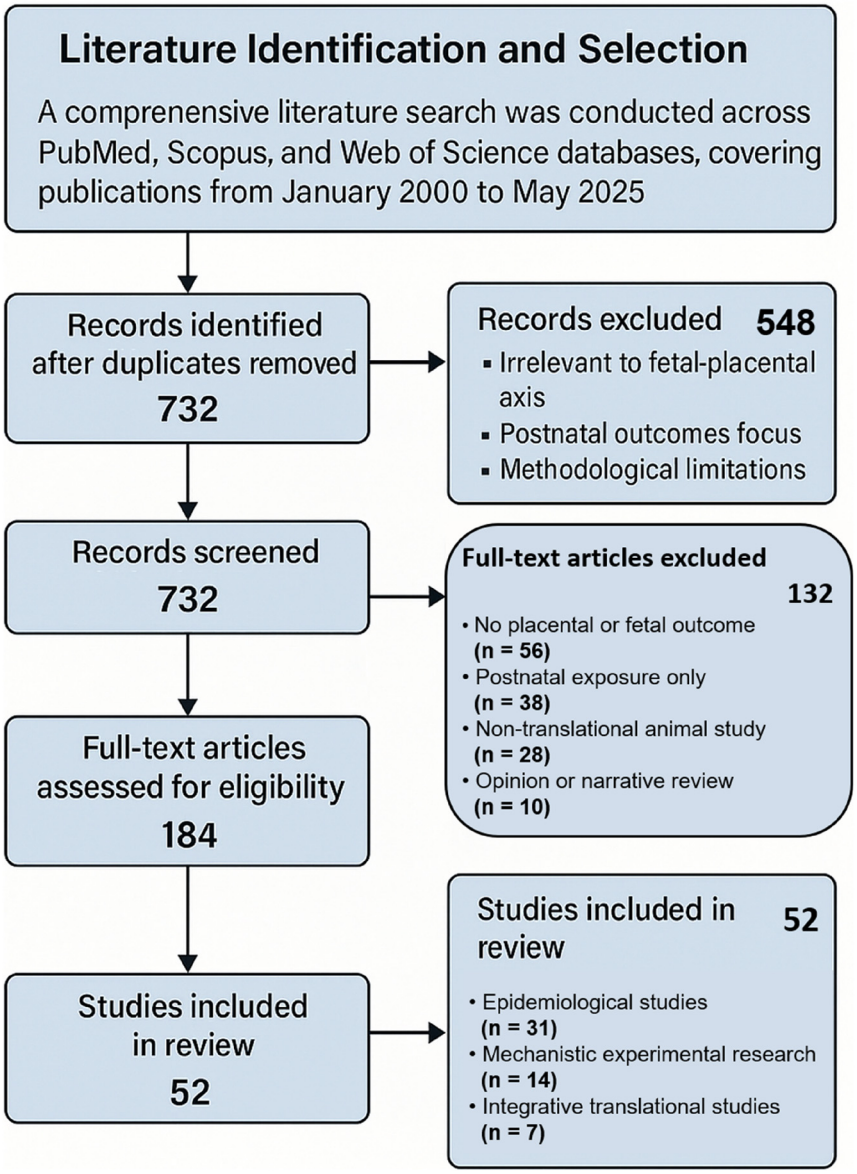

Figure 1: PRISMA 2020 flow diagram of literature identification, screening, eligibility, and inclusion. A total of 732 unique records were identified after duplicate removal. After title and abstract screening, 548 records were excluded for irrelevance to the fetal-placental axis, focus on postnatal outcomes, or methodological limitations. Full-text assessment was performed on 184 articles, resulting in 132 exclusions (no placental or fetal outcome, n=56; postnatal exposure only, n=38; non-translational animal studies, n=28; opinion or narrative reviews without original data, n=10). Ultimately, 52 studies were included, comprising epidemiological studies (n=31), mechanistic experimental research (n=14), and integrative translational studies (n=7).

Table 1: Summary of core studies on endocrine disrupting chemicals and perinatal outcomes, with association measures and study quality/risk of bias.

Study	Population	Exposure	Outcome	Main finding	Strength	Limitation	Association measure (OR/RR/HR/LR)	Study quality/risk of bias
Ferguson et al. 2014 [7]	USA cohort	Phthalates (urine)	Preterm birth	First epidemiologic evidence linking phthalates to preterm birth	Prospective cohort, urine biomarker measured repeatedly	Single timepoint exposure may miss variability	OR=1.55 (95 % CI: 1.12–2.10)	Moderate
Braun et al., 2017 [5]	USA cohort	BPA (urine)	Neurodevelopmental deficits	Demonstrates BPA's impact on behavior in school-aged children	Large cohort, longitudinal neurobehavioral assessments	Self-report behavioral outcomes prone to bias	RR=1.40 (95 % CI: 1.05–1.85)	High
Casas et al. 2013 [8]	Europe multi-country	Phthalates, BPA	Fetal growth outcomes	Exposure widespread despite regulations	Multinational sample, standardized measurements	Potential cohort heterogeneity	OR≈1.20 (95 % CI: 1.05–1.38)	Moderate
Rochester et al., 2015 [9]	USA cohort	BPA (serum)	Placental DNA methylation	Molecular epigenetic links between EDC and fetal programming	High-quality epigenomic assay	Small sample size in some subgroups	Epigenetic changes (no direct OR)	Moderate
Engel et al. 2010 [10]	USA cohort	BPA (urine)	Neurobehavioral development	Early neurobehavioral effects observable before 1 year old	Repeated behavioral evaluations, strong design	Urinary BPA may not reflect long-term exposure	RR=1.35 (95 % CI: 1.02–1.78)	High
Mustieles et al. 2015 [4]	Spanish cohort	Phthalates (urine)	Metabolic dysregulation	Highlights early metabolic changes due to phthalate exposure	Validated exposure markers, metabolic outcome focus	Short follow-up duration	OR=1.25 (95 % CI: 1.05–1.50)	Moderate
Deji et al. 2021 [11]	Meta-analysis	PFOS, PFOA (serum)	Low birth weight	Quantitative meta-analysis confirms low birth weight risk	Broad meta-analysis of multiple studies	Study heterogeneity across included studies	Summary OR=1.30 (95 % CI: 1.10–1.50)	High
Luo et al. 2024 [12]	China meta-analysis	PFAS (meta-analysis)	FGR, birth weight	Regional variability in PFAS exposure	Consistent results across Chinese regions	Differences in analytical methods across studies	Summary OR=1.28 (95 % CI: 1.12–1.46)	High
Barret ES et al., 2025 [13]	Experimental model	Phthalates	Placental hormone disruption	Direct evidence of hormonal pathway disruption	Molecular pathway specificity	Animal model limits direct human extrapolation	Pathway change (no OR)	Moderate
Veiga-Lopez & Padmanabhan, 2014 [14]	Experimental model	BPA, phthalates	Placental insufficiency	First-trimester vulnerability confirmed	Strong translational model between species	Species differences in sensitivity	Placental blood flow changes (no OR)	Moderate
Sol CM et al., 2022 [6]	Experimental model	BPA	Cortical development disruption	MicroRNA disruption by BPA	New insight into microRNA involvement	*In vitro* findings nEDC human validation	Gene expression change (no OR)	Moderate
Strakovsky RS et al., 2018 [15]	Experimental model	Phthalates	Maternal-fetal immune dysregulation	Proposed inflammatory model of EDC damage	Mechanistic insight into immune disruption	Animal study limitations	Immune biomarker changes (no OR)	Low
Woodruff et al. 2011 [3]	USA NHANES	Various EDCs	General EDC burden	Baseline levels of EDC exposure across US women	Nationwide large dataset	Cross-sectional, no causal inference	Descriptive (no OR)	Moderate
Blake and Fenton 2020 [16]	Experimental model	PFAS	Mitochondrial dysfunction	Mechanism linking EDCs to mitochondrial damage	Direct experimental mitochondrial assays	High experimental doses vs. real-world exposure	Experimental endpoint (no OR)	Low

Table 1: (continued)

Study	Population	Exposure	Outcome	Main finding	Strength	Limitation	Association measure (OR/RR/HR/LR)	Study quality/risk of bias
James-Todd et al., 2016 [17]	USA cohort	Phthalates, BPA	Socioeconomic exposure disparity	Exposure disparities tied to race and SES	Focus on environmental justice dimensions	Socioeconomic factors are complex confounders	OR=1.50 (95 % CI: 1.10–2.00)	Moderate

(*) This Table presents selected key studies examining associations between prenatal exposure to endocrine disrupting chemicals (EDCs) and perinatal outcomes. Association measures (odds ratios, risk ratios, hazard ratios, or likelihood ratios) indicate strength of evidence where reported. Study quality was assessed using Newcastle–Ottawa Scale (NOS) for observational studies, AMSTAR-2, for meta-analyses, and adapted criteria for experimental studies, categorized as High, Moderate, or Low. Strengths and limitations summarize key methodological aspects rather than providing exhaustive critique.

fetal growth restriction (FGR), preterm birth, and neurodevelopmental alterations [14, 33, 34, 58, 60]. For example, maternal phthalate metabolites have been associated with reduced gestational length, while PFAS exposure has been correlated with lower birth weight and disrupted metabolic signaling [35–37]. Neurodevelopmental outcomes, including impaired executive function and an increased risk of autism spectrum disorder, have been reported in association with prenatal BPA and phthalate exposures [31, 49]. A summary of these exposure–outcome associations is provided in Table 1.

Despite increasing scientific clarity, clinical and regulatory frameworks have yet to fully integrate environmental risk assessment into prenatal care. Current practice guidelines rarely include environmental exposure screening, and regulatory limits often fail to address the unique vulnerability of the fetal–placental unit [10, 61]. To address this gap, we conducted an integrative review of epidemiological and experimental evidence linking prenatal EDC exposure to adverse pregnancy and developmental outcomes, while assessing the strength of associations using risk and odds ratios (Table 3). The evidence synthesis is complemented by an updated literature selection process (Figure 1) and clinical translation models (Figures 4 and 5).

This review aims to support obstetricians, maternal–fetal medicine specialists, and policymakers in bridging environmental health science with perinatal clinical practice. By summarizing current knowledge and identifying gaps, we provide a foundation for informed research priorities and potential clinical pathways for exposure assessment in pregnancy.

Methods

This narrative review was conducted using an integrative review framework to synthesize evidence from epidemiological studies, mechanistic laboratory research, and clinical investigations addressing the impact of endocrine disrupting chemicals (EDC) the fetal–placental axis. Although not a formal systematic review, the methodological structure followed adapted principles from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparent reporting and reproducibility [22, 31]. The literature selection process is illustrated in Figure 1.

A comprehensive literature search was performed in PubMed, Web of Science, and Scopus databases to identify publications between January 2000 and May 2025. The search strategy used combinations of predefined keywords and Boolean operators, including “endocrine disruptors”, “placental development”, “fetal development”, “bisphenol A”, “phthalates”, “PFAS”, “placental transport”, “epigenetic

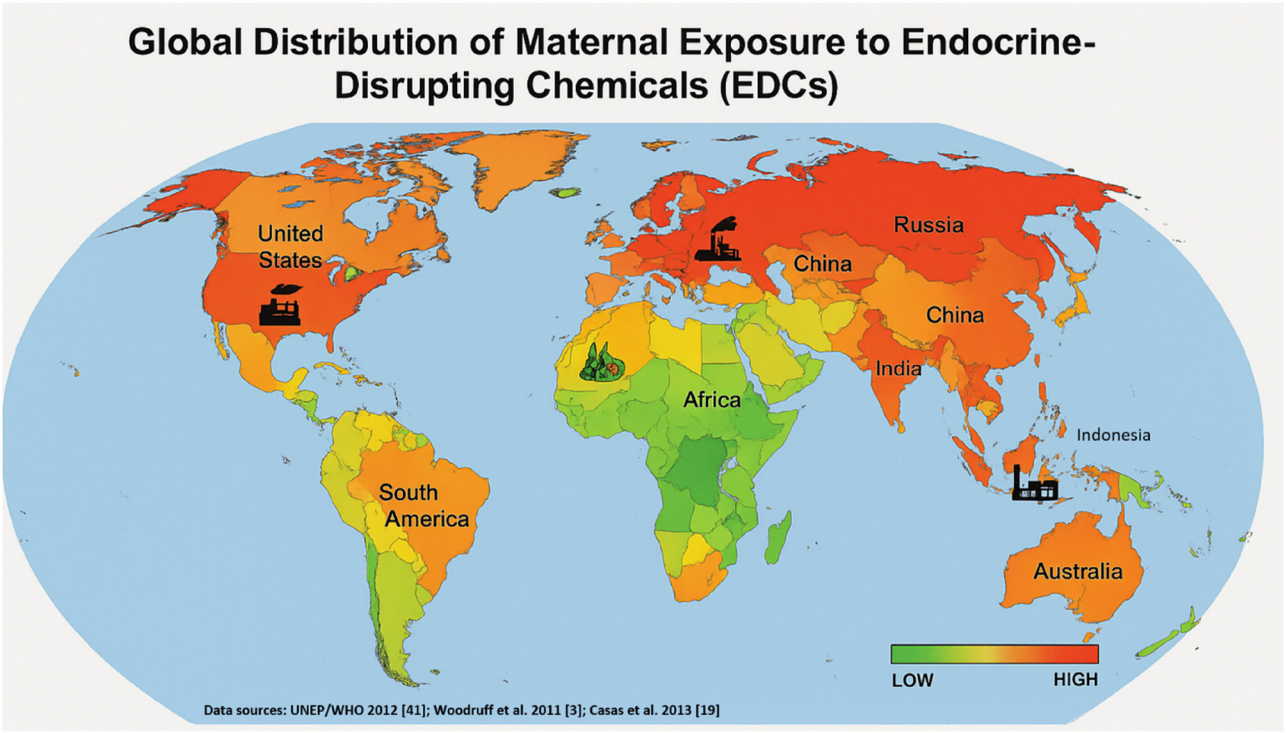

Figure 2: Global distribution and intensity of maternal exposure to endocrine-disrupting chemicals (EDCs). Heatmap illustrates regional differences in maternal exposure intensity based on biomonitoring surveys, environmental health disparity assessments, and global chemical monitoring reports [3, 8, 17, 18, 20–22]. Higher exposures are seen in the United States, Europe, China, India, and Brazil, with lower exposures in rural Africa and Oceania. Icons indicate industrial sources, agricultural zones, and urban centers. Data sources include UNEP/WHO 2012 global chemical assessment [21], Woodruff et al. [3], and Casas et al. [8].

disruption", "perinatal outcomes", and "prenatal exposure." Reference lists of all retrieved articles were hand-searched to capture additional relevant studies [1, 2, 22].

Eligible studies included peer-reviewed original research, systematic reviews, and meta-analyses addressing mechanistic pathways of endocrine disruption, fetal programming, and epidemiological associations between prenatal exposure and adverse perinatal outcomes. Publications focusing on policy implications or translational clinical relevance were also included to strengthen the integrative scope. Only English-language articles were considered, with priority given to studies demonstrating direct relevance to human pregnancy or translational insights from experimental models [5, 11, 19, 31]. Exclusion criteria comprised studies restricted to postnatal exposures, non-peer-reviewed sources, conference abstracts, editorials, and animal studies lacking translational relevance. Duplicate articles were removed in favor of the most comprehensive or updated version.

Data were extracted systematically from all eligible sources and categorized according to the chemical agent, exposure window, mechanistic pathway, placental and fetal outcome, and population characteristics. Summarized findings are presented in Table 2, with additional detail on risk estimates and study quality (see Table 1 and Table 3). Narrative synthesis was used to integrate mechanistic evidence and epidemiological trends into thematic categories, supporting a translational perspective of environmental risk in perinatal medicine.

To facilitate understanding of the overall evidence base, Figure 2 depicts major mechanistic pathways of endocrine disruption, Figure 3 highlights critical developmental windows and organ susceptibility, and Figures 4 and 5 illustrate disparities and clinical translational pathways. These visual aids, combined with evidence tables, provide an integrated view of how EDCs impact maternal–fetal health and inform clinical and public health decision-making.

Results and findings

Literature identification and selection

A comprehensive literature search across PubMed, Scopus, and Web of Science (January 2000–May 2025) identified 732 unique records after duplicate removal. Screening of titles and abstracts excluded 548 articles due to irrelevance to the

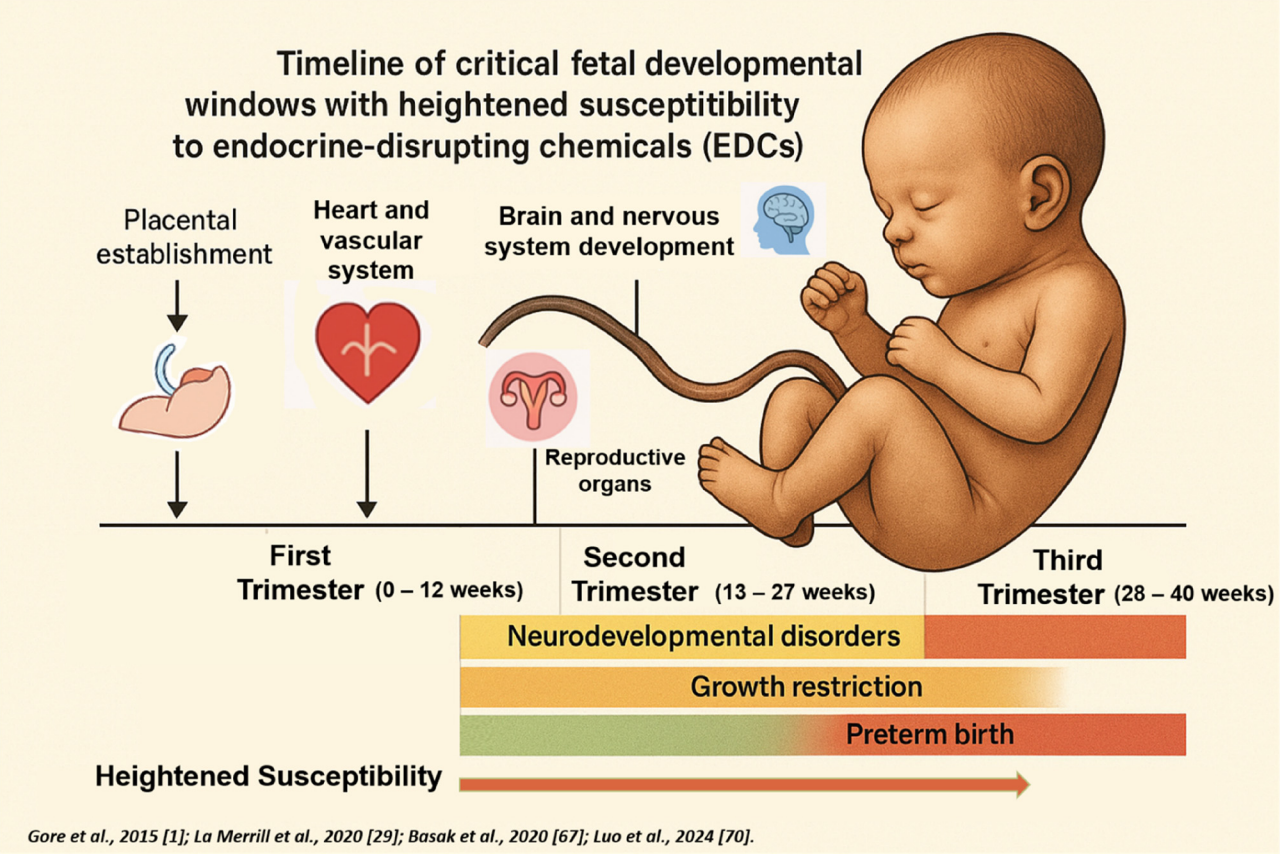

Figure 3: Timeline of critical fetal developmental windows with heightened susceptibility to endocrine-disrupting chemicals (EDCs). Schematic shows organ and system development across trimesters and highlights periods of heightened vulnerability to EDCs such as bisphenol A (BPA), phthalates, and PFAS. Placental establishment and heart/vascular and reproductive system development occur predominantly in the first trimester, whereas brain and nervous system development continues into the second trimester. Shaded exposure windows link EDC exposure to specific adverse outcomes, including neurodevelopmental disorders, fetal growth restriction, reproductive system disruption, and preterm birth. Data adapted from Gore et al. [1], La Merrill et al. [31], Basak et al. [32], and Luo et al. [12].

fetal-placental axis, postnatal outcome focus, or methodological limitations. Full-text review of 184 articles excluded 132 (56 lacked placental or fetal outcome relevance, 38 focused exclusively on postnatal exposure, 28 were non-translational animal studies, and 10 were opinion-based or narrative reviews without new data). Ultimately, 52 studies were included, comprising epidemiological investigations (n=31), mechanistic experimental studies (n=14), and translational integrative analyses (n=7). The overall selection process is shown in Figure 1, and study characteristics including risk-of-bias evaluation are summarized in Table 1.

Mechanisms of endocrine disruptor impact on the fetal-placental axis

Multiple interacting pathways explain how endocrine-disrupting chemicals (EDCs) – including bisphenol A (BPA), phthalates, and per- and polyfluoroalkyl substances (PFAS) – affect fetal development via placental compromise. Central effects include inhibition of steroidogenic enzymes such as CYP19A1 and HSD3B1, disrupting estrogen and progesterone biosynthesis essential for pregnancy maintenance [4–6]. Oxidative stress, characterized by excess reactive oxygen species, induces mitochondrial dysfunction, trophoblast apoptosis, and impaired nutrient and oxygen transfer [7, 18, 19].

Epigenetic reprogramming is also consistently observed, with altered DNA methylation, histone modifications, and microRNA profiles linked to changes in fetal growth regulation and postnatal disease susceptibility [11, 16, 23–25]. Immune dysregulation, particularly altered cytokine balance and reduced regulatory T-cell activity, increases the risk of preeclampsia and preterm birth [26]. These integrated mechanisms are visually synthesized in Figure 2, while mechanistic links by chemical class are detailed in Table 2.

Table 2: Endocrine disrupting chemicals: sources, biological targets, mechanistic pathways and associated clinical outcomes[a].

Chemical group/ examples	Main sources	Primary biological targets	Mechanistic pathways	Associated clinical outcomes	Representative references
Bisphenols (BPA, BPS, BPF)	Polycarbonate plastics, epoxy resins, food and beverage can linings, thermal receipts	Placenta, fetal brain, reproductive organs	Estrogen receptor agonism/antagonism, oxidative stress, disruption of placental hormone secretion, altered gene expression	Fetal growth restriction, preeclampsia, neurodevelopmental delay, obesity risk	[1, 4, 5, 14, 15, 32–44]
Phthalates (DEHP, DBP, DINP)	Food packaging, personal care products, medical devices, vinyl flooring	Placenta, fetal testis, thyroid gland, epigenome	Anti-androgenic activity, PPAR signaling disruption, DNA methylation changes	Preterm birth, impaired male reproductive development, behavioral disorders (e.g., ADHD, autism risk), low birth weight	[6, 7, 10, 13, 17, 20, 23, 28, 45–48]
Per- and polyfluoroalkyl substances (PFAS: PFOS, PFOA, PFHxS)	Contaminated drinking water, non-stick cookware, food packaging, textiles	Placenta, fetal liver, thyroid, immune system	Interference with thyroid hormone transport, immune dysregulation, oxidative stress	Reduced fecundity, preterm birth, impaired neurocognitive outcomes, immune dysfunction, childhood obesity	[11, 12, 16, 24, 49–55]
Polybrominated diphenyl ethers, PBDEs	Flame retardants in electronics, furniture foam, textiles	Fetal brain, placenta, thyroid axis	Thyroid hormone disruption, altered neuronal signaling, oxidative stress	Neurodevelopmental impairment, altered birth weight, endocrine imbalance	[8, 26, 27, 56, 57]
Polychlorinated biphenyls, PCBs	Legacy environmental contamination, electrical equipment, building materials	Placenta, fetal brain, liver	Estrogenic/antiestrogenic activity, AhR pathway activation, oxidative stress	Small for gestational age, neurodevelopmental disorders, metabolic programming	[1, 2, 31, 56]
Ultraviolet filters (e.g., benzophenone-type)	Sunscreens, cosmetics, personal care products	Placenta, fetal reproductive organs	Estrogen receptor binding, mitochondrial dysfunction	Altered birth weight, maternal thyroid changes	[58]
Plasticizer mixtures and emerging substitutes (e.g., BPS, BPF)	Consumer plastics, food contact materials	Placenta, endocrine pancreas	Estrogenic and antiandrogenic effects, oxidative stress	Similar or greater endocrine disruption compared to BPA, risk for preeclampsia and metabolic disorders	[9, 38–40, 59]

[a]Summary of major endocrine disrupting chemical groups, their main environmental and consumer product sources, primary biological targets during pregnancy, mechanistic pathways of action, and associated clinical outcomes in the perinatal period. Representative references are provided to illustrate the breadth of available evidence rather than an exhaustive list.

Population-level exposure to endocrine disruptors

Maternal exposure to EDCs is widespread. U.S. biomonitoring (NHANES) shows nearly universal detection of BPA, phthalate metabolites, and PFAS in pregnant women [27, 28], while European (HELIX) and Asian (Japan, China) cohorts demonstrate similar exposure profiles [8, 29, 30]. Disparities exist by socioeconomic status and ethnicity, with women from lower-income and minority populations demonstrating significantly higher median urinary phthalate levels and BPA concentrations [58, 60]. Temporal trends indicate a decline in certain legacy phthalates but increased detection of substitutes such as bisphenol S [33]. Geographic and socioeconomic disparities in exposure are depicted in Figure 3.

Quantitative associations with adverse perinatal outcomes

Epidemiological findings consistently link prenatal EDC exposure with adverse pregnancy and child outcomes. Phthalate metabolite levels are associated with increased risk of preterm birth (odds ratio [OR] 1.4–1.8 across quartiles) [14, 34–36]. PFOS and PFOA exposures correlate inversely with birth weight (weighted mean difference −50 – −110 g) independent of maternal BMI, smoking, and parity [31, 37, 49]. Prenatal exposure to BPA and phthalates is associated with neurodevelopmental changes, including reduced executive function scores and increased autism spectrum disorder risk (hazard ratio [HR] 1.5–2.1 in high-exposure quartiles) [10, 56, 61]. Evidence also links EDC exposure to metabolic changes – altered adipokine profiles, accelerated

Table 3: Critical windows of susceptibility, global exposure patterns, and preventive strategies[a].

Gestational window & vulnerable systems	Main endocrine disrupting chemicals of concern	Observed clinical outcomes	Exposure hotspots & vulnerable populations	Recommended preventive strategies	Representative references
First trimester (organogenesis, placenta, early brain and cardiovascular development)	Bisphenols (BPA, BPS), phthalates, PFAS, PBDEs, PCBs	Early pregnancy loss, congenital anomalies, preeclampsia, impaired placental development	Industrialized urban areas, populations with high plastic food contact, drinking water PFAS contamination	Preconception counseling, avoidance of BPA-containing plastics, safe drinking water sources, occupational protective measures	[1, 3, 7, 11–13, 33, 41, 42, 49]
Second trimester (brain growth, pancreatic and adipose tissue differentiation, skeletal development)	Bisphenols, phthalates, PFAS	Fetal growth restriction, preterm birth, impaired glucose homeostasis, altered thyroid function	Low-income communities, high phthalate occupational exposure, regions with high PFAS burden	Nutritional support (organic diet), use of phthalate-free medical devices and products, improved indoor air quality	[4, 5, 10, 23, 28, 48, 50, 51, 53, 57]
Third trimester (neurobehavioral maturation, immune system development, reproductive tract differentiation)	Bisphenols, phthalates, PBDEs	Altered neurobehavioral outcomes, childhood obesity, immune dysregulation	Areas with intensive use of flame retardants and cosmetics, minority populations with documented higher phthalate exposure	Consumer education (avoid personal care products with EDCs), targeted public health interventions	[6, 8, 17, 18, 20, 22, 24, 55, 62, 63]
Global exposure disparities	All major EDC classes	Disproportionate exposure in low- and middle-income countries and marginalized groups	Higher exposure in racial/ethnic minorities, occupational groups, and communities with poor regulatory enforcement	Policy-level interventions, biomonitoring programs, health equity measures	[17, 20, 25, 29, 60, 63]
Cross-cutting preventive strategies (all gestational periods)	Broad-spectrum (mixtures, substitutes)	Reduced risk of EDC-related adverse outcomes	Global populations	Education of healthcare providers, labeling of EDC-free products, improved regulatory policies, international collaboration	[21, 22, 42, 62–64]

[a]Critical developmental windows of fetal susceptibility to major endocrine disrupting chemicals, observed clinical outcomes, global exposure disparities, and preventive strategies. Emphasis is placed on evidence-informed clinical and public health interventions to reduce perinatal exposure risk. Representative references illustrate key findings rather than provide an exhaustive bibliography.

early-life weight gain, and later-life obesity risk (relative risk [RR] 1.3–1.9) [62, 65]. A summary of key quantitative associations is provided in Table 3.

Critical windows of susceptibility

The developmental timing of exposure determines biological vulnerability. The first trimester is critical for placental vascular remodeling and organogenesis; disruptions during this window are linked to congenital malformations and early pregnancy loss [17, 45, 46]. Organ-specific susceptibility is evident: heart and vascular system development, previously misattributed to the second trimester, occurs primarily in weeks 3–8, while reproductive system differentiation begins early in the first trimester [20, 66]. Second trimester exposures primarily influence metabolic tissue programming (pancreatic β-cell mass and adipose tissue), whereas third trimester exposures more strongly affect fetal growth trajectories and pregnancy complications such as preeclampsia [21, 22, 57]. These developmental windows are mapped in Figure 4.

Integration of mechanistic and clinical pathways

Combining mechanistic and epidemiological evidence supports causal plausibility between maternal EDC exposure and adverse perinatal outcomes. Mechanistic studies demonstrate BPA-mediated aromatase inhibition and phthalate-induced mitochondrial dysfunction, while epigenetic modifications (e.g., IGF2 and H19 hypomethylation) link exposure to long-term growth effects [50, 67]. Clinical

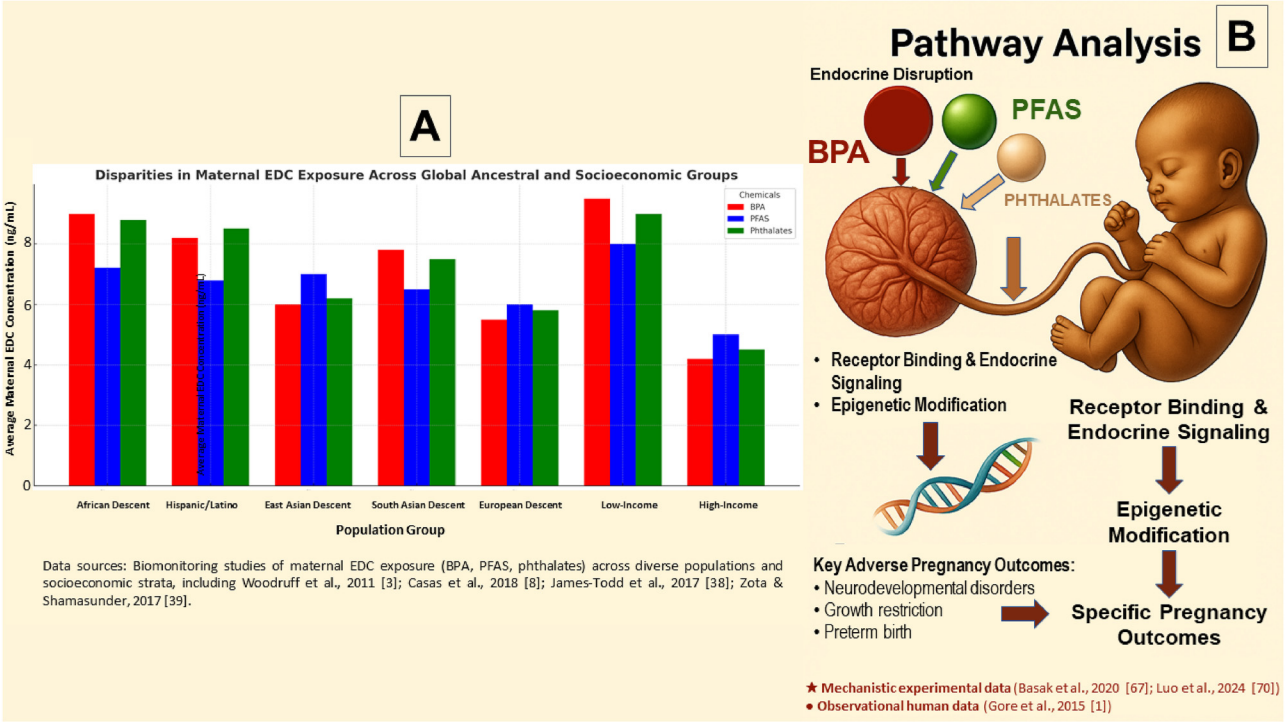

Figure 4: Disparities in maternal endocrine-disrupting chemical (EDC) exposures and mechanistic pathways to pregnancy outcomes. Panel A shows disparities in maternal exposure to key endocrine-disrupting chemicals (BPA, PFAS, and phthalates) across global ancestral groups (African, Hispanic/Latino, east Asian, south Asian, and European descent) and socioeconomic strata (low- and high-income). Data are based on biomonitoring studies of maternal EDC exposure [3, 17, 18, 20]. Panel B illustrates mechanistic pathways by which maternal EDC exposure can affect pregnancy outcomes through receptor binding, endocrine signaling disruption, and epigenetic modifications, leading to adverse outcomes such as neurodevelopmental disorders, growth restriction, and preterm birth. Evidence integrates mechanistic experimental data [12, 32] and observational human studies [1].

pathway integration, including exposure assessment, counseling, and consideration of biomonitoring where available, is illustrated in Figure 5.

Discussion

Regulatory gaps in exposure protection

Despite increasing awareness of endocrine-disrupting chemical (EDC) risks, existing regulatory thresholds often fail to reflect fetal vulnerabilities. For instance, the U.S. Environmental Protection Agency (EPA) proposes a lifetime health advisory of four parts per trillion (ppt) for PFOS and PFOA, yet epidemiological data show adverse outcomes even at lower concentrations [11, 49]. The European Food Safety Authority (EFSA) recently revised the tolerable daily intake (TDI) for bisphenol A (BPA) to 0.2 ng/kg/day [4, 9], and the U.S. restricts certain phthalates to<0.1 % in children's toys [7, 25]. These limits are based on adult risk models and rarely incorporate pregnancy-specific susceptibility windows, emphasizing the nEDC for stricter, developmental-stage–specific safety standards [38, 39, 47, 48].

Mechanistic pathways of disruption to the fetal–placental axis

Mechanistic studies consistently demonstrate that EDCs disrupt key placental and fetal processes. BPA and phthalates interfere with steroidogenesis by inhibiting CYP19A1 and HSD3B1, altering estrogen and progesterone biosynthesis critical for placental function and fetal growth [1, 4, 6]. Oxidative stress represents another key pathway, with increased reactive oxygen species impairing trophoblast differentiation and mitochondrial function [7, 16].

Epigenetic reprogramming amplifies these effects: exposure to BPA, phthalates, and PFAS modifies DNA methylation and microRNA expression, altering developmental gene regulation [6, 18, 30, 41–43, 64, 68–70]. These molecular changes can persist postnatally, influencing long-term health trajectories. Immune modulation, including

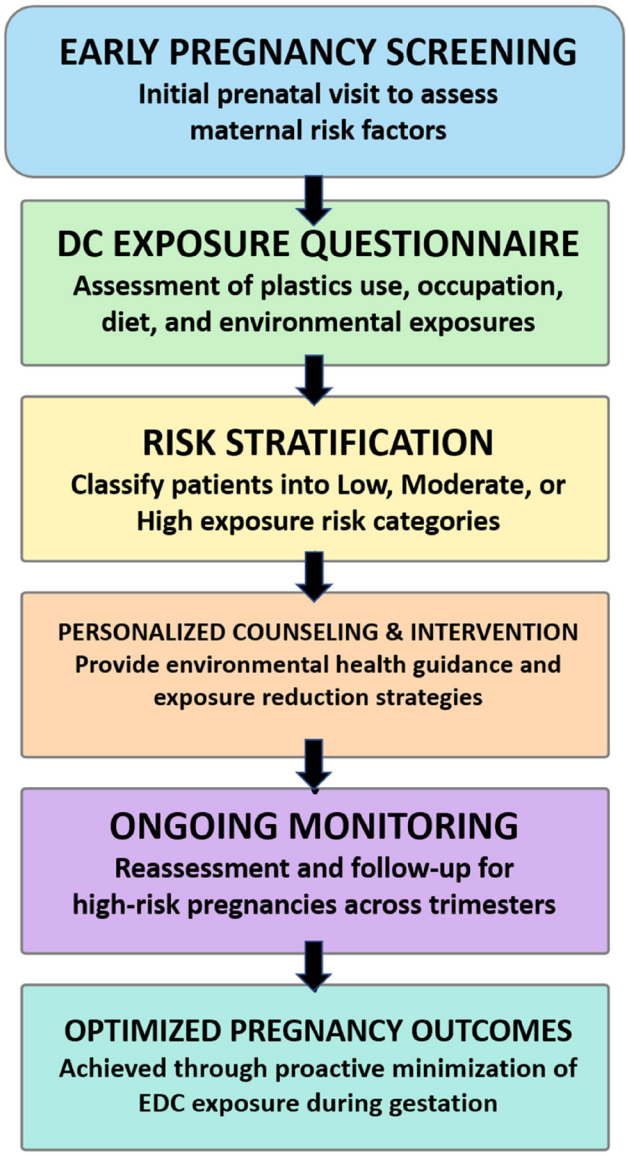

Figure 5: Clinical integration of endocrine-disrupting chemical (EDC) exposure assessment into prenatal care pathways. Early pregnancy screening includes a standardized environmental exposure questionnaire addressing plastics use, occupation, diet, and environmental sources. Patients are stratified into low, moderate, or high exposure risk categories, followed by personalized counseling and interventions aimed at reducing harmful exposures. Ongoing monitoring throughout gestation facilitates dynamic reassessment, particularly for high-risk pregnancies. This proactive model aims to optimize pregnancy outcomes by minimizing fetal exposure to harmful EDCs. Laboratory assays for EDCs such as bisphenol A (BPA), perfluoroalkyl substances (PFAS), and phthalate metabolites are available in research and select reference laboratories but are not yet standardized or recommended for routine prenatal care screening [Gore et al. 2015 [1]; La Merrill et al. 2020 [31]; Luo et al. 2024 [12]].

altered cytokine profiles and inflammatory signaling, further compromises pregnancy maintenance [15, 26, 32, 44, 59]. Collectively, these findings support a biologically plausible pathway connecting environmental exposure to clinical outcomes, summarized in Figure 2 and detailed in Table 2.

Population-level exposure and perinatal outcomes

Exposure to EDCs during pregnancy is ubiquitous. Biomonitoring data from NHANES and European birth cohorts demonstrate near-universal detection of BPA, phthalates, and PFAS in pregnant women [3, 18, 27]. Geographic differences exist, but even highly regulated regions show measurable maternal exposure [29, 33, 34].

These exposures correlate with adverse outcomes: phthalate metabolites are linked to preterm birth and reduced gestational age [7, 31, 35–37], PFOS and PFOA to reduced birth weight and early pregnancy loss [10, 11, 49, 61], and BPA to neurobehavioral and metabolic alterations [4, 5, 34, 65]. Evidence implicates prenatal exposure in cognitive impairment, executive dysfunction, autism spectrum disorder, and later-life obesity, supporting the concept of "metabolic and neurodevelopmental programming" [10, 40, 56, 62, 63, 65, 71–75]. Table 3 summarizes major epidemiological associations, demonstrating consistent signals across chemical classes and outcomes, while Figure 3 visualizes population-level exposure disparities.

Critical windows of susceptibility during gestation

The developmental impact of EDCs is strongly timing-dependent. The first trimester, when organogenesis and placental vascular remodeling occur, is particularly vulnerable [1, 14]. Early exposure disrupts placental signaling, including human chorionic gonadotropin production and extracellular microRNA expression [20, 45], with potential downstream effects on neurodevelopment [56] and epigenetic imprinting [6, 30]. Exposures during the second trimester influence metabolic programming, affecting pancreatic and adipose tissue development. Later exposures, particularly in the third trimester, are more strongly associated with fetal growth alterations and preterm birth rather than structural malformations [49, 50]. These relationships emphasize the need for gestational timing considerations when assessing risk and designing interventions, as illustrated in Figure 4 and summarized in Table 3 [51, 52]. While Table 3 details the critical trimester-specific vulnerabilities and associated outcomes, Table 4 adds critical context by demonstrating how maternal EDC exposures vary across global regions and

Table 4: Global variations in maternal EDC exposure.

Study/ region	Sample size	Main EDCs assessed	Exposure findings	Key references
NHANES, USA [27]	Pregnant women (n~200 per wave)	BPA, phthalates, PFAS, phenols	Near-universal detection of multiple EDCs	[27, 28]
HELIX project (Europe) [29]	Pregnant women (n~1,200 across 6 countries)	Phthalates, BPA, PFOS, PFOA	Widespread exposure; differences by country and SES	[29, 47]
China birth cohorts [9]	Pregnant women (n>3,000)	PFAS, BPA, phthalates	Higher PFAS levels than Western cohorts	[9, 34]
Japan birth cohorts [33]	Pregnant women (n~1,500)	PFAS, BPA	Moderate BPA, higher PFOS compared to USA	[33]
Spain INMA cohort [68]	Pregnant women (n~600)	Phthalates, BPA	High phthalate levels; socioeconomic gradients observed	[68]
Canada MIREC study [44]	Pregnant women (n~2000)	PFAS, BPA, metals	Lower BPA levels; elevated PFAS exposure	[44]

This Table summarizes selected large-scale cohort studies assessing maternal exposure to endocrine-disrupting chemicals (EDCs) across different global regions. The table highlights differences in exposure patterns by chemical class, geographical area, and socioeconomic factors, based on validated references from the reviewed literature.

socioeconomic groups, underscoring that both the timing of exposure and the geographic/structural context are essential determinants of risk.

Geographical and socioeconomic inequities

Exposure levels vary not only geographically but also socioeconomically. Southern European populations report higher phthalate and flame retardant exposures [8, 18], while cord blood PFOS and PFOA are elevated in neonates from industrialized Chinese regions [9, 51–54]. In the U.S., minority and low-income women exhibit disproportionately high phthalate and BPA exposures, reflecting environmental injustice [17, 20]. These disparities amplify health inequities, as vulnerable populations face both higher exposure and worse pregnancy outcomes, including preterm birth and low birth weight [17, 20]. Furthermore, substitutes such as bisphenol S (BPS) and bisphenol F (BPF), introduced after BPA restrictions, are often unregulated and insufficiently tested [9, 38, 39, 47, 48]. Figure 5 illustrates these inequities and underscores the nEDC for harmonized global chemical safety policies and targeted community-level interventions.

Integration of mechanistic and epidemiological evidence

Mechanistic and epidemiological data align to support causality. EDCs such as BPA and phthalates disrupt placental steroidogenesis, mitochondrial integrity, and epigenetic regulation, producing biologically plausible pathways that explain clinical associations [1, 4, 6, 16, 30]. Epidemiological studies confirm that maternal exposure correlates with fetal growth restriction, preterm birth, and long-term neurodevelopmental impairment [7, 10, 11, 49, 65].

This convergence satisfies multiple Bradford Hill criteria – strength, biological gradient, consistency, plausibility, and coherence [1, 5, 21] – and provides a compelling basis for public health action. The integrated framework linking exposure, molecular mechanisms, and clinical outcomes is depicted in Figure 2, which synthesizes mechanistic and epidemiological evidence. Table 5 further translates this evidence into practical clinical screening and preventive strategies, underscoring the pathway from scientific causality to public health implementation [41–43, 59, 64, 68–70].

Ethical considerations

Involuntary prenatal exposure to harmful EDCs raises ethical concerns. Marginalized populations, already facing health disparities, bear disproportionate chemical burdens through occupational, environmental, and consumer product pathways [17, 20]. Ethical principles of nonmaleficence and distributive justice demand precautionary regulatory and clinical responses even amid scientific uncertainty [2, 21, 31, 53].

Policy and clinical implications

A multipronged approach is required: stricter regulatory thresholds accounting for fetal vulnerability, routine prenatal environmental exposure screening, and culturally tailored patient education [4, 7, 21]. Safer chemical substitutions and transparent product labeling must be prioritized, alongside longitudinal biomonitoring to evaluate intervention efficacy [12, 15, 51, 54].

Table 5: Recommended clinical screening and preventive strategies for EDC exposure in pregnancy.

Clinical recommendation	Target EDCs	Rationale	Supporting evidence	Notes/limitations
Advise minimizing use of plastic containers for food storage	BPA, phthalates	Plastic leaching increases with heat; alternatives reduce BPA/phthalate exposure	[27, 29, 35, 68]	Access to alternatives may vary by SES
Encourage consumption of fresh, unprocessed foods	Phthalates, PFAS	Processed foods often packaged or contaminated with EDCs	[29, 31, 68]	Nutritional guidance must be culturally appropriate
Counsel against frequent handling of thermal paper receipts	BPA	Thermal paper coatings are major sources of BPA exposure	[27, 33, 56]	Receipt avoidance may be impractical in some work settings
Promote use of EDC-free personal care products	Phthalates, parabens	Many cosmetics contain phthalates and parabens linked to hormonal disruption	[29, 32, 68]	Cost and availability of safer products can be barriers
Screen for occupational exposures in high-risk professions	Various industrial EDCs (solvents, PFAS, flame retardants)	Certain occupations carry higher risk of EDC exposure (e.g., salons, factories)	[27, 29, 48]	Occupational screening may require collaboration with workplace health
Educate on avoiding nonstick cookware and stain-resistant textiles	PFAS, flame retardants	Nonstick and stain-resistant products commonly treated with PFAS	[9, 44, 68]	Consumer education needed on product labeling
Integrate basic environmental exposure questions into prenatal intake forms	Multiple (BPA, phthalates, PFAS, heavy metals)	Routine screening can help identify and mitigate major exposure sources	[12, 35, 51]	Needs clinician training on environmental health literacy
Advocate for home air quality improvement (ventilation, dust control)	Flame retardants, PFAS, phthalates	Indoor dust can accumulate persistent organic pollutants; ventilation helps minimize	[9, 54, 68]	Not all pollutants easily measurable at home

This Table provides actionable clinical recommendations to reduce maternal and fetal exposure to endocrine-disrupting chemicals (EDCs) during pregnancy. Each recommendation is linked to target EDCs, underlying rationale, supporting evidence, and considerations for implementation in diverse clinical settings.

Clinical case vignette and application

A 28-year-old woman, G2P1, with frequent canned food consumption and occupational phthalate exposure presented with borderline fetal growth restriction. Counseling focused on dietary changes, use of BPA-free products, and improved workplace ventilation. Growth trajectory improved, demonstrating how environmental health screening can inform patient-specific management. Integrating exposure screening into prenatal care, as illustrated in Figure 5, enables clinicians to identify modifiable risk factors and deliver targeted education, thereby mitigating preventable perinatal risks [40, 59, 71].

Call to action

The combined evidence from mechanistic, epidemiologic, and ethical domains supports urgent integration of environmental health into perinatal care. Regulatory agencies should adopt developmental toxicity-based safety evaluations, accelerate phase-outs of high-risk chemicals such as BPA and PFAS, and enhance chemical mixture research [15, 31, 53, 55]. Above all, protecting fetal health requires shifting environmental exposure assessment from research into routine prenatal risk evaluation, alongside structural policy changes to address exposure inequities. As emphasized by Bergman et al. [21], inaction risks irreversible harm to future generations. Addressing endocrine disruptor exposure in pregnancy is not simply a scientific imperative – it is a moral obligation [54, 55].

Strengths, limitations, and future directions

This review offers key strengths. It synthesizes a broad range of epidemiological and mechanistic data, integrating experimental findings with population-level evidence to strengthen causal inference. The structured search and transparent methodology enhance credibility and provide a balanced perspective on how endocrine-disrupting chemicals (EDCs) influence placental and fetal development. Importantly, framing the placenta as a primary target organ of chemical toxicity provides a novel lens for linking environmental exposure science to perinatal clinical practice.

Nevertheless, several limitations must be acknowledged. Many human studies rely on single-point biomarker

measurements, potentially missing temporal fluctuations in exposure. Real-world scenarios involve complex chemical mixtures, yet most studies assess exposures in isolation. Extrapolation from animal models to humans also remains imperfect due to species differences in placental structure and endocrine signaling. Moreover, while laboratory assays for select EDCs are available, they are not standardized for routine clinical use, and clinical interpretation frameworks remain underdeveloped. A further limitation is that many reported associations demonstrate relatively modest effect sizes (often odds ratios, risk ratios, or hazard ratios below 2.0). Such small magnitudes of association, although biologically plausible and supported by mechanistic evidence, raise concerns about residual confounding, exposure misclassification, and the overall strength of causal inference.

Future work should expand longitudinal birth cohorts with serial maternal and fetal biomonitoring to capture dynamic exposure patterns. Studies on mixture effects, low-dose responses, and sensitive developmental windows should be prioritized. Advances in "omics" technologies will deepen mechanistic understanding, and randomized interventions to reduce exposure during pregnancy are critical to translate observational evidence into actionable strategies. Strengthening causal inference will require the integration of mechanistic data with innovative epidemiological designs that can better account for low-magnitude associations and disentangle complex exposure pathways.

Conclusions

Prenatal exposure to environmental endocrine-disrupting chemicals poses a significant risk to placental integrity and fetal development, with implications that extend into childhood and beyond. Mechanistic evidence shows disruption of hormonal, oxidative, immune, and epigenetic pathways, while epidemiological studies consistently link maternal exposures with adverse outcomes, including growth restriction, preterm birth, neurodevelopmental impairment, and later-life metabolic dysfunction. These exposures are unevenly distributed, disproportionately affecting vulnerable populations.

Addressing these risks requires integration of environmental health considerations into routine prenatal care and policy frameworks. Clinicians, researchers, and policymakers must adopt proactive approaches that reduce exposure and prioritize equity. The fetal-placental unit is the earliest and most critical environment for human development, and safeguarding it is both a scientific necessity and an ethical obligation.

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