

Review

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The relationship between emerging contaminants and gestational diabetes mellitus: a review

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Abstract

Emerging contaminants (ECs) have garnered growing attention as potential contributors to adverse metabolic outcomes during pregnancy, particularly gestational diabetes mellitus (GDM). Despite increasing recognition of their endocrine-disrupting capabilities, the precise relationship between EC exposure and glucose dysregulation in the gestational context remains inadequately characterized. The scarcity of longitudinal human studies, along with limited mechanistic elucidation, highlights a critical gap in understanding how these ubiquitous environmental pollutants may perturb maternal metabolic homeostasis. This review consolidates current epidemiological evidence linking key classes of ECs, including per- and polyfluoroalkyl substances (PFAS), polychlorinated biphenyls (PCBs), phthalates (PAEs), bisphenols, organochlorine pesticides (OCPs), parabens, and alkylphenols, with GDM risk and impaired glycemic control. Parallel examination of *in vivo* and *in vitro* studies reveals plausible biological mechanisms, including oxidative stress, mitochondrial dysfunction, inflammatory signaling, and insulin resistance (IR), through which these compounds may mediate their effects. By integrating data across human and experimental research domains, this review underscores the urgent need for high-resolution exposure assessments, mixture toxicity frameworks, and mechanistic validation. Such insight is essential for advancing etiological understanding, informing regulatory action, and guiding preventive strategies to mitigate the impact of environmental exposures on maternal-fetal metabolic health.

Keywords: Gestational diabetes mellitus, emerging contaminants, human exposure, glucose metabolism, mechanisms



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INTRODUCTION

Gestational diabetes mellitus (GDM) is a form of glucose intolerance first identified during pregnancy and is among the most common complications affecting maternal health (see [Supplementary Table 1](#) for abbreviations)^[1]. According to the 2024 IDF Diabetes Atlas, hyperglycemia affects nearly one in five pregnancies worldwide, and GDM increases the risk of adverse outcomes such as preterm birth, macrosomia, and cesarean delivery^[2]. Furthermore, it poses long-term health risks, including a higher likelihood of developing type 2 diabetes (T2DM) and metabolic disorders in both mothers and their children^[3]. Known risk factors for GDM include advanced maternal age, obesity, family history of diabetes, and excessive gestational weight gain. However, emerging evidence suggests that environmental exposures, particularly to emerging contaminants (ECs), may also contribute to its development^[4–11].

ECs refer to chemicals or materials that pose a potential or recognized threat to human health or the environment^[12]. These substances are typically not regulated or lack established health standards, and their presence is increasing in various environmental matrices^[12,13]. ECs include persistent organic pollutants, pharmaceuticals and their metabolites, personal care products, nanomaterials, and microplastics^[14]. Due to their resistance to degradation, many ECs persist in water, soil, and air, and are difficult to remove through conventional treatment methods. For example, a study has detected pharmaceuticals and personal care products (PPCPs) in surface water, seawater, groundwater, and wastewater treatment plants in the Middle East and North Africa region^[15]. These contaminants enter the human body primarily through ingestion, inhalation, or skin contact^[15]. Despite often being present at low concentrations, the biotoxicity, environmental persistence, and bioaccumulation of these substances raise significant concerns.

Recent studies have started to explore the relationship between EC exposure and the development of GDM. However, most of these studies have focused on individual pollutants or their congeners, often within the context of either epidemiological studies or animal models. A comprehensive review encompassing a broad spectrum of ECs, integrating both epidemiological findings and experimental data, is currently lacking.

This review aims to provide a systematic summary of epidemiological studies on the impact of seven major types of ECs: PFAS, PCBs, PAEs, bisphenols, OCPs, parabens, and alkylphenols, examining their effects on glucose metabolism, insulin resistance (IR), and the development of GDM. In cases where relevant, insights from experimental studies are included to illuminate potential mechanisms of action. By integrating diverse evidence, this review contributes to a holistic understanding of the environmental factors influencing GDM and provides a scientific foundation for future research and policy development.

PER- AND POLYFLUOROALKYL SUBSTANCES

Per- and polyfluoroalkyl substances (PFAS) are a group of synthetic chemicals, including perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), perfluorononanoic acid (PFNA), perfluorohexanesulfonic acid (PFHxS), and perfluorodecanoic acid (PFDA)^[16]. These substances are widely used in consumer products such as carpets, textiles, firefighting foams, sunscreens, and cosmetics^[17]. They are also applied as coating agents in paper and cardboard packaging materials^[17]. Due to the strong stability of the carbon-fluorine bond, PFAS exhibit exceptional chemical and thermal stability^[18]. As a result, they persist in the environment and are frequently detected in multiple environmental matrices, including water, soil, and vegetation^[19]. PFAS are also commonly found in human samples, such as urine, blood, breast milk, amniotic fluid, and other tissues^[20,21]. Human exposure to PFAS occurs primarily through ingestion of contaminated food and drinking water^[22]. Given their widespread use and persistence, PFAS are increasingly recognized as significant environmental contaminants. However, the full extent of their health impacts, particularly in relation to metabolic disorders such as GDM, remains an area of ongoing research.

Epidemiological studies

Epidemiological evidence on the association between PFAS exposure and the risk of GDM remains inconsistent; relevant studies are summarized in Table 1^[5,9,23-44]. In a cross-sectional study in China, researchers measured the concentrations of 13 PFAS in umbilical cord blood and found that exposure to several PFAS, including perfluoroheptanoic acid (PFHpA), PFNA, and perfluorobutanesulfonic acid (PFBS), was significantly associated with elevated mid-pregnancy blood glucose levels^[23]. Similarly, a study conducted in Hong Kong identified PFOS and PFOA as the predominant PFAS compounds, with concentrations in late pregnancy higher than those reported in other studies^[5]. Both PFAS mixtures and individual compounds were significantly associated with elevated maternal levels of HbA1c and 2-hour plasma glucose (2h-PG)^[5].

A total of seven case-control studies were reviewed, with six consistently finding a positive association between PFAS exposure and the risk of GDM^[24-30]. For instance, a study by Xu *et al.* enrolled 165 GDM cases and 330 controls and found that elevated levels of PFBS and perfluorododecanoic acid (PFDoA) in early pregnancy were significantly associated with an increased risk of GDM^[25]. In a study analyzing maternal serum samples collected 1-2 days before delivery, PFOA, PFOS, perfluoroundecanoic acid (PFUnDA), PFDoA, and 6:2 chlorinated polyfluorinated ether sulfonic acid (6:2 Cl-PFESA) were found to be positively associated with GDM risk, while 4:2 Fluorotelomer sulfonate (4:2 FTS), 6:2 Fluorotelomer sulfonate (6:2 FTS), PFHxS, and ammonium 4,8-dioxo-3H-perfluorononanoate (ADONA) showed negative associations^[27]. Similarly, case-control studies conducted in other regions reported comparable findings. A study conducted in the United States reported significant positive associations between PFOA, PFOS, and other PFAS compounds in early and mid-pregnancy and the risk of GDM^[28].

Despite the heterogeneity in findings, the majority of cohort studies have reported a positive association between PFAS exposure and the risk of GDM^[9,31-44]. A study by Rahman *et al.* reported that, among pregnant women with a family history of T2DM, higher maternal plasma levels of PFNA, PFOA, PFHpA, and PFDoDA in early pregnancy were positively associated with the risk of GDM^[9]. Similarly, Ren *et al.* investigated the relationship between maternal plasma concentrations of PFAS in early pregnancy and blood glucose levels, and found that PFNA, PFDA, perfluoroundecanoic acid (PFUdA), and PFDoA were positively associated with 1-hour plasma glucose (1h-PG) levels^[39]. However, some studies reported inverse associations, such as the one conducted by Mehta *et al.*, which found that PFAS exposure was inversely associated with fasting glucose, fasting insulin, and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR)^[40].

In summary, while the epidemiological evidence remains inconclusive, the majority of studies suggest that PFAS exposure may be a potential environmental risk factor for GDM. Further prospective studies and mechanistic research are necessary to validate these associations and clarify the underlying biological mechanisms.

Experimental studies and possible mechanisms

Emerging experimental evidence indicates that PFAS, particularly PFOS and PFBS, may impair pancreatic β -cell function and insulin secretion through oxidative stress, mitochondrial dysfunction, and key signaling pathway alterations. *In vivo* and *in vitro* studies showed that PFOS exposure reduced pancreas weight, islet size, and serum insulin levels in male mice, and decreased viability and glucose-stimulated insulin release of β -TC-6 cells. High-dose PFOS induced ROS accumulation, leading to apoptosis and necrosis^[45]. Collectively, these findings support a potential causal link between PFOS exposure and increased diabetes risk^[45]. Similarly, adult male Balb/c mice orally administered 1.25 mg/kg PFOA for 28 days exhibited elevated fasting blood glucose (FBG) levels, reduced hepatic glycogen and glucose content, and alterations in key

Table 1. Summary of epidemiological evidence on the association between PFAS exposure and GDM

Study type	Year	Biological sample			Population		Findings (GM/Med, ng/mL)	Author
		Analyte	Matrix	Gestational week	Country	Size		
Cross-sectional	2020	PFAS	Umbilical cord blood	At delivery	China	874	Positive association with increased blood glucose in 2nd trimester: PFHpA [0.04], PFNA [0.27], and PFBS [0.04] ^a	Li et al. ^[23]
Cross-sectional	2024	PFAS	Serum	24-32 weeks of gestation	China	1,601	PFAS mixture and its individual components were associated with higher maternal HbA1c and 2h-PG	Yang et al. ^[5]
Case-control	2018	PFAS	Serum	1-2 days before delivery	China	252	Positive association with postpartum fasting glucose: 1m-PFOS [0.14 vs. 0.14], 3m + 4m-PFOS [0.44 vs. 0.42], 5m-PFOS [0.36 vs. 0.36], PFHxS [0.48 vs. 0.47] ^b	Wang et al. ^[24]
Case-control	2020	PFAS	Serum	16-20 weeks of gestation	China	495	Positive association between PFBS [0.17 vs. 0.13], PFDoA [0.19 vs. 0.08] and GDM ^b	Xu et al. ^[25]
Case-control	2021	PFAS	Serum	1st trimester	China	231	Higher PFHxS [0.025 vs. 0.015] levels in GDM cases ^c	Liu et al. ^[26]
Case-control	2022	PFAS	Serum	1-2 days before the delivery	China	340	Positive association with GDM: PFOA [22.6 vs. 2.32], PFOS [5.98 vs. 3.29], PFUnDA [2.90 vs. 1.06], PFDoA [0.250 vs. 0.175] and 6:2Cl-PFESA [5.30 vs. 2.38] Negative association with GDM: 4:2FTS [0.150 vs. 0.250], 6:2FTS [0.050 vs. 0.050], PFHxS [0.150 vs. 1.03] and ADONA [0.175 vs. 0.150] ^b	Xu et al. ^[27]
Case-control	2023	PFAS	Serum	1st and 2nd trimester	USA	128	Positive association with GDM in 1st and 2nd trimester: PFDA [0.09; 0.07], PFNA [0.39; 0.35], and PFOA [0.71; 0.69] ^b	Peterson et al. ^[28]
Case-control	2023	PFAS	Serum	1st trimester	China	590	Positive association between PFOA [10.3 vs. 9.52], PFHpS [0.09 vs. 0.08] and GDM A nonlinear association between 6:2Cl-PFESA [3.93 vs. 3.68] and GDM ^b	Zang et al. ^[29]
Case-control	2023	PFAS	Serum	1st trimester	China	204	Positive association with GDM: PFOA [5.22 vs. 5.03], PFNA [0.48 vs. 0.48], PFHxS [0.45 vs. 0.43] and 6:2 Cl - PFESA [2.58 vs. 2.42] ^b	Zhang et al. ^[30]
Cohort	2015	PFAS	Serum	NA	USA	258	Positive association between PFOA [3.94 vs. 3.07] and GDM ^a	Zhang et al. ^[31]
Cohort	2016	PFAS	Plasma	1st trimester	Canada	1,274	Positive association between PFHxS [1.00 vs. 1.02] and IGT ^a	Shapiro et al. ^[32]
Cohort	2017	PFAS	Plasma	1st trimester	Spain	1,240	Positive association between PFOS [5.77], PFHxS [0.55] and IGT ^a	Matilla-Santander et al. ^[33]
Cohort	2017	PFAS	Serum	20-34 weeks of gestation	USA	628	Negative association with maternal fasting glucose: PFOA [1.04], PFNA [0.39], PFDeA [0.14], PFHxS [0.75] ^a	Starling et al. ^[34]
Cohort	2017	PFAS	Serum	34 weeks of gestation	Denmark	604	No association	Valvi et al. ^[35]
Cohort	2018	PFAS	Serum	11 gestational week	Denmark	318	Positive association between PFHxS [0.30] and increased fasting glucose, fasting insulin and HOMA-IR Positive association between PFNA [0.66] and higher fasting insulin and HOMA-% β ^b	Jensen et al. ^[36]
Cohort	2018	PFAS	Serum	1st trimester	China	385	Positive association between PFOA [7.3] and FIns, HOMA-IR, 1h-PG, 2h-PG Negative association between PFOS [5.4] and averaged FBG and OGTT blood glucose ^b	Wang et al. ^[37]
Cohort	2019	PFAS	Plasma	8–13 weeks of gestation	USA	2,292	Positive association with GDM in T2DM family history: PFNA [0.80], PFOA [1.99], PFHpA [0.08], PFDoDA [0.06] ^a	Rahman et al. ^[9]
Cohort	2020	PFAS	Plasma	1st trimester	USA	1,540	Positive association between PFOS [25.5] and 1h-GCT levels A nonlinear association between MeFOSAA [1.9] and 1h-GCT levels ^a	Preston et al. ^[38]
Cohort	2020	PFAS	Plasma	1st trimester	China	981	Positive association with 1h-PG: PFNA [1.8],	Ren et al. ^[39]

							PFDA [2.0], PFUdA [1.6], PFDoA [0.1] ^a	
Cohort	2021	PFAS	Serum	Late 1st or 2nd trimester	USA	95	All PFAS [5.81] was negatively associated with fasting glucose, fasting insulin, and HOMA-IR ³	Mehta et al. ^[40]
Cohort	2021	PFAS	Serum	16 and 26 weeks of gestation	USA	388	No association	Yuong et al. ^[41]
Cohort	2021	PFAS	Plasma	1st trimester	China	2,747	Positive association between PFBS [0.045 vs. 0.035], PFHpA [0.061 vs. 0.054] and GDM; Positive association with 1h-PG and 2h-PG: PFOS [9.41 vs. 9.40], PFNA [1.61 vs. 1.65], PFHxS [0.54 vs. 0.53], PFHpA [0.061 vs. 0.054] ^b	Yu et al. ^[42]
Cohort	2023	PFAS	Plasma	1st trimester	China	1,405	Higher PFOA and PFHxS and lower PFUA in high FPG group	Wang et al. ^[43]
Cohort	2024	PFAS	Serum	Median 17 weeks gestation	USA	452	All PFAS (except Me-PFOSA-AcOH) were negatively associated with insulin, HOMA-IR, and leptin	Cinzori et al. ^[44]

^aConcentrations reported as geometric means (GM). ^bConcentrations reported as medians (Med). PFAS: Per- and polyfluoroalkyl substances; GDM: gestational diabetes mellitus; HbA1c: hemoglobin A1c; OGTT: oral glucose tolerance test; FBG: fasting blood glucose; 1h-PG: 1-hour plasma glucose; 2h-PG: 2-hour plasma glucose; T2DM: type 2 diabetes mellitus; IGT: impaired glucose tolerance; HOMA-IR: homeostasis model assessment of insulin resistance; HOMA-%β: homeostasis model assessment of β-cell function; PFOA: perfluorooctanoic acid; PFOS: perfluorooctane sulfonate; PFHpA: perfluoroheptanoic acid; PFNA: perfluorononanoic acid; PFBS: perfluorobutanesulfonic acid; 1m-PFOS: 1-monomethyl isomer of PFOS; 3m + 4m-PFOS: 3- and 4-monomethyl isomers of PFOS; 5m-PFOS: 5-monomethyl isomer of PFOS; PFDA: perfluorodecanoic acid; PFHpS: perfluoroheptane sulfonate; PFHxS: perfluorohexane sulfonate; PFDoA: perfluorododecanoic acid; PFHxA: perfluorohexanoic acid; PFUnDA: perfluoroundecanoic acid; 6:2Cl-PFESA: 6:2 chlorinated polyfluoroether sulfonic acid; 4:2FTS: 4:2 fluorotelomer sulfonate; ADONA: ammonium 4,8-dioxa-3H-perfluorononanoate; PFDeA: perfluorodecanoic acid; ("Both PFDA and PFDeA are used in the literature to denote perfluorodecanoic acid.") PFUdA: perfluoroundecanoic acid; MeFOSAA: 2-(N-methyl-perfluorooctane sulfonamido) acetate; Me-PFOSA-AcOH: 2-(N-methyl-perfluorooctane sulfonamido) acetic acid.

metabolic enzyme activities such as decreased glycogen synthase activity and increased glucose-6-phosphatase activity^[46]. Together, these findings suggest that PFOA may promote hepatic glycogen breakdown and elevate glucose export from the liver into the bloodstream, while also enhancing the downstream glycolytic pathway and the tricarboxylic acid cycle^[46].

PFOS exposure has similarly been associated with impaired glucose metabolism, particularly during developmental stages. Pregnant CD-1 mice exposed to PFOS during gestation and lactation gave birth to offspring that exhibited glucose metabolism disturbances in early life, with later exacerbation of IR and glucose intolerance, especially when exposed to a high-fat diet^[47]. These findings imply that early-life PFOS exposure may predispose offspring to long-term metabolic vulnerabilities^[47].

Moreover, studies involving Sprague-Dawley rats have demonstrated that gestational exposure to low doses of PFOS induces glucolipid metabolic disorders through disruption of peroxisome proliferator-activated receptor signaling and alterations in glycerolipid and glycolysis pathways^[48]. Altered gene expression and metabolite changes, including glycerol 3-phosphate and lactosylceramide, have been observed^[48].

Another study in pregnant rats found that high-dose PFBS exposure (50 mg/kg bw-d) significantly reduced 1h-PG and the OGTT (Oral Glucose Tolerance Test) area under the curve, suggesting altered glucose homeostasis^[49]. Integrated transcriptomics and metabolomics revealed changes in pathways related to xenobiotic metabolism, glutathione metabolism, bile acid secretion, pyruvate metabolism, and the citric acid cycle. Key differentially expressed genes (e.g., *Gstm1*, *Gck*, *Ppp1r3c*) and metabolites (e.g., fumaric acid, L-lactic acid) were linked to glucolipid metabolic regulation^[49]. These findings indicate that gestational PFBS exposure may disrupt glucose metabolism at the molecular level, potentially increasing the risk of abnormal glucose tolerance^[49].

Although the PFAS family includes many compounds such as PFNA and PFHxS, mechanistic evidence in animal experiments is currently most extensive for PFOA, PFOS, and PFBS. These studies suggest that PFAS exposure, particularly during critical developmental windows, may lead to persistent metabolic disruptions by targeting hepatic enzyme function, nuclear receptor signaling, and intermediary metabolism. Although experimental doses are higher than typical environmental exposures, they provide valuable mechanistic insights into PFAS-induced β -cell dysfunction, impaired insulin secretion, and glucose dysregulation.

POLYCHLORINATED BIPHENYLS

Polychlorinated biphenyls (PCBs) are synthetic organochlorine compounds composed of two linked benzene rings with varying chlorine substitutions^[50]. Historically, PCBs were widely applied as plasticizers and in industrial coolants^[50]. Due to their chemical stability, lipophilicity, and resistance to degradation, PCBs persist in the environment and bioaccumulate through the food chain^[51]. Despite being banned under the United States Toxic Substances Control Act in 1979, their extensive use and environmental persistence have led to continued detection in air, soil, water, and biological matrices, including human blood and breast milk^[52,53]. Human exposure occurs through multiple pathways, including diet, inhalation, dust ingestion, and dermal absorption^[54]. The widespread presence and long half-life of PCBs have raised considerable public health concerns, prompting extensive research into their potential toxicological effects.

Epidemiological studies

Relatively few studies have investigated the relationship between PCBs and GDM, with existing research primarily adopting a prospective cohort design. These epidemiological studies are summarized in Table 2^[6,9,26,32,35,40,55–59]. These studies typically assess PCB exposure levels in pregnant women using maternal serum samples, focusing on early pregnancy and its potential impact on glucose metabolism disorders. For instance, a cross-sectional study conducted in the United States with 254 participants explored the association between serum PCB levels before pregnancy and GDM, but no significant relationship was found^[55]. In contrast, a case-control study in China conducted by Zhang *et al.* measured serum PCB levels during the first trimester and identified a significant positive association between PCB-52 and GDM^[56]. Higher levels of PCB-52 were linked to elevated glucose concentrations across all OGTT values^[56]. Another cohort study in Canada also measured serum PCB levels in early pregnancy but found no significant association with the risk of GDM^[32].

Overall, the epidemiological evidence on the relationship between PCB exposure and GDM risk remains inconsistent. While some studies have identified a positive association, others have found no significant relationship. This suggests the need for more large-scale, multicenter studies to clarify the potential biological mechanisms and dose-response relationships of PCB exposure during pregnancy, a physiologically vulnerable period for endocrine disruption, in relation to the development of GDM.

Experimental studies and possible mechanisms

Experimental studies provide insight into potential biological mechanisms linking PCBs to glucose metabolic dysfunction. PCB-126, a coplanar PCB congener, may disrupt the crosstalk between adipose tissue and skeletal muscle, particularly under insulin-resistant conditions. One *in vitro* study used a co-culture model to examine how PCB-126 affects adipokine secretion from adipocytes, and whether these adipocyte-derived factors alter glucose metabolism and mitochondrial function in myotubes^[60]. The study found that PCB-126 exposure led to increased adipokine secretion from IR adipocytes, impairing glucose uptake in co-cultured myotubes^[60]. These results highlight the crucial role of adipose-to-muscle communication in mediating PCB-126-induced metabolic abnormalities, particularly under insulin-

Table 2. Summary of epidemiological evidence on the association between PCBs, PAE exposure and GDM

Study type	Year	Biological sample		Gestational week	Population		Findings (GM/Med)	Author
		Analyte	Matrix		Country	Size		
Cross-sectional	2020	PCBs	Serum	Before pregnancy	USA	254	No association	Neblett et al. ^[55]
Case-control	2016	PCBs	Serum	3rd trimester	Iran	140	Positive association with GDM: total PCBs [3.09 vs. 1.60 ng/g lipid], Ln PCB-187 [0.03 vs. 0.01 ng/g lipid], Ln PCB-118 [0.03 vs. 0.01 ng/g lipid] Negative association with GDM: Ln PCB-28 [0.02 vs. 0.01 ng/g lipid] ^{a,d}	Eslami et al. ^[57]
Case-control	2018	PCBs	Serum	1st trimester	China	231	Positive association between PCB-52 [2.0 vs. 1.5 pg/mL] and GDM, all blood glucose values of OGTT ^b	Zhang et al. ^[56]
Case-control	2021	PCBs	Serum	1st trimester	China	231	Higher PCB-52 [1.98 vs. 1.45 pg/g], PCB-101 [1.40 vs. 0.99 pg/g] levels in GDM cases ^b	Liu et al. ^[26]
Case-Control	2023	PCBs	Serum	1st trimester	China	208	Positive association between PCB-153 [0.96 vs. 0.59 ng/g lipid], Σ PCB [3.57 vs. 2.61 ng/g lipid] and GDM, 1h-PG ^b	Ma et al. ^[6]
Cohort	2016	PCBs	Serum	Before pregnancy	USA	258	Negative association with GDM after adjustment for total serum lipids: PCB-138 [0.03 ng/g serum], PCB-153 [0.0423 ng/g serum], PCB-156 [0.0054 ng/g serum], PCB-167 [0.0000 ng/g serum], PCB-170 [0.0127 ng/g serum], PCB-172 [0.0000 ng/g serum], PCB-178 [0.0017 ng/g serum], PCB-180 [0.0320 ng/g serum], and PCB-194 [0.0064 ng/g serum] ^b	Jaacks et al. ^[58]
Cohort	2016	PCBs	Plasma	1st trimester	Canada	1,274	No association	Shapiro et al. ^[32]
Cohort	2017	PCBs	Serum	1st trimester	Greece	939	Positive association with GDM [Σ PCBs 360.1 vs. 290.8 pg/mL] ^a	Vafejadi et al. ^[59]
Cohort	2017	PCBs	Serum	34 weeks of gestation	Denmark	604	No association	Valvi et al. ^[35]
Cohort	2019	PCBs	Plasma	8-13 weeks of gestation	USA	2,292	Positive association between PCBs with ≥ 6 chlorine atoms and GDM	Rahman et al. ^[9]
Cohort	2021	PCBs	Serum	Late 1st or 2nd trimester	USA	95	Positive association between individual PCBs and fasting insulin, HOMA-IR	Mehta et al. ^[40]
Cross-sectional	2015	PAEs	Urine	Averaged 12.8 weeks of gestation	USA	72	No association	Robledo et al. ^[66]
Cross-sectional	2020	PAEs	Meconium	At the first 24h after delivery	China	251	Positive association between MiBP [24.05 ng/g], MnBP [26.64 ng/g], MEHP [51.82 ng/g] and GDM in women with male fetuses ^a	Guo et al. ^[71]
Cross-sectional	2022	PAEs	Urine	1st trimester	China	200	Higher MEHP [4.25 vs. 2.71 μ g/L] levels in GDM cases ^b	Liang et al. ^[75]
Case-control	2016	PAEs	Urine	Clinic visit 1, 2, 3, 4	USA	350	Positive association between MEP and IGT Negative association between DEHP and IGT	James-Todd et al. ^[68]
Case-control	2022	PAEs	Urine	Visit 1, 2, 3, 4	USA	606	1st trimester: Negative association between MBP [11.60 ng/mL], MCNP [2.41 ng/mL], MCPPE [2.31 ng/mL] and IGT ^a 2nd trimester: Negative association between MCNP [1.98 ng/mL], MCPPE [1.90 ng/mL] and IGT; Positive association between MiBP [5.84 ng/mL], MHBP [1.23 ng/mL]	James-Todd et al. ^[74]

							and IGT ^a	
Case-control	2023	PAEs	Serum	At the time of delivery	China	201	Positive association between MBP [3.52 vs. 3.37 ng/mL], MiBP [0.86 vs. 0.57 ng/mL] and 2h-PG, GDM ^b	Wang <i>et al.</i> ^[76]
Cohort	2015	PAEs	Urine	1st trimester	Canada	1,274	No association	Shapiro <i>et al.</i> ^[67]
Cohort	2018	PAEs	Urine	1st and 2nd trimester	USA	245	Positive association between MEP [60.2 ng/mL] and glucose levels Negative association between MiBP [5.7 ng/mL] and glucose levels ^{a,c}	James-Todd <i>et al.</i> ^[69]
Cohort	2019	PAEs	Urine	1st and 3rd pregnancy	USA	705	Positive association between T1T3avg MEP and GDM	Shaffer <i>et al.</i> ^[70]
Cohort	2021	PAEs	Urine	1st, 2nd, 3rd trimester	China	3,269	Positive association with blood glucose, GDM	Gao <i>et al.</i> ^[72]
Cohort	2021	PAEs	Urine	1st and 2nd trimester	USA	315	No association	Zukin <i>et al.</i> ^[73]
Cohort	2024	PAEs	Urine	1st trimester	China	725	Positive association between MBZP and GDM	Guo <i>et al.</i> ^[77]
Cohort	2024	PAEs	Urine	2nd trimester	USA	298	Positive association between DEHP and fasting glucose, fasting insulin, and HOMA2-IR	Peng <i>et al.</i> ^[7]

^aConcentrations reported as geometric means (GMs). ^bConcentrations reported as medians (Med). ^cConcentrations of PAE metabolites were SG-adjusted (specific gravity-adjusted) to account for variations in urine dilution, ensuring comparable exposure estimates. ^dValues in brackets are original concentrations (not log-transformed). PCB: Polychlorinated biphenyl; PAE: phthalate; GDM: gestational diabetes mellitus; GM: geometric mean; Med, median; Σ PCBs: sum of PCB congeners; MiBP: monoisobutyl phthalate; MnBP: mono-n-butyl phthalate; MEHP: mono(2-ethylhexyl) phthalate; MEP: monoethyl phthalate; DEHP: di(2-ethylhexyl) phthalate; MBP: monobutyl phthalate; MCNP: mono-(3-carboxypropyl) phthalate; MCPP: mono-(3-carboxypropyl) phthalate; MHBP: mono-(3-hydroxybutyl) phthalate; MBZP: monobenzyl phthalate; FBG: fasting blood glucose; OGTT: oral glucose tolerance test; 1h-PG: 1-hour plasma glucose; 2h-PG: 2-hour plasma glucose; HOMA-IR: homeostatic model assessment of insulin resistance; HOMA2-IR: updated homeostatic model assessment of insulin resistance; IGT: impaired glucose.

resistant conditions.

An *in vivo* study using female Institute of Cancer Research mice also investigated the effects of PCB-126 exposure during the nursing period on glucose tolerance and body composition in offspring^[61]. The results showed that maternal PCB-126 exposure did not significantly alter short- or long-term body composition in offspring but did lead to impaired glucose tolerance (IGT) in early life^[61]. Importantly, these impairments were transient and largely reversible as the offspring matured^[61]. These findings suggest that PCB-126 may induce early-life metabolic disturbances, which could predispose offspring to long-term metabolic issues.

In summary, PCBs, particularly PCB-126, may disrupt glucose metabolism through multiple pathways, including adipose-to-muscle signaling dysfunction and early-life programming effects, especially under conditions of IR or during developmental windows of vulnerability.

PHTHALATES

Phthalates (PAEs) are among the most widely used plasticizers, with ortho-phthalates being the most common types, including diethyl phthalate (DEP), dibutyl phthalate (DBP), diisobutyl phthalate (DIBP), diisononyl phthalate (DINP), and di(2-ethylhexyl) phthalate (DEHP)^[62]. Since their introduction in the 1930s, PAEs have been extensively applied in the plastics industry to enhance the flexibility and elasticity of rigid polymers^[63]. They are commonly used as additives and solvents in pharmaceuticals, cosmetics, and personal care products^[64]. Due to their ability to leach from products, PAEs are readily absorbed by humans and are metabolized into monoesters, which are primarily excreted in urine, though they can also be detected in other bodily fluids and tissues^[65]. As endocrine disruptors, PAEs have been identified as potential risk factors for various diseases, including GDM, due to their ability to interfere with hormone signaling pathways that regulate glucose metabolism.

Epidemiological studies

A total of thirteen epidemiological studies have investigated the relationship between PAE exposure and GDM, including three cross-sectional studies, three case-control studies, and seven prospective cohort studies [Table 2]^[7,66-77]. Most of these studies focused on maternal urine samples to assess exposure levels to various PAEs and their metabolites, with exposure timing varying across studies, from early to late pregnancy. For example, a cross-sectional study by Guo *et al.* in China analyzed meconium samples collected within the first 24 h after birth to assess *in utero* PAE exposure and its association with GDM^[71]. The study found a positive association between levels of Mono-isobutyl phthalate (MiBP), Mono-n-butyl phthalate (MnBP), and Mono (2-ethylhexyl) phthalate (MEHP) in meconium and GDM risk, particularly among women carrying male fetuses^[71]. A recent case-control study by Wang *et al.* in China, which analyzed serum samples collected at delivery from 201 postpartum women, also reported positive associations between serum levels of MBP and MiBP and GDM occurrence, as well as elevated 2h-PG levels during the OGTT^[76]. In contrast, a cohort study by Zukin *et al.* in the United States, which measured urinary phthalate metabolite levels during early and mid-pregnancy, found no significant association between PAE exposure and GDM risk^[73].

Overall, the epidemiological evidence suggests that PAE exposure may be associated with maternal glucose dysregulation and increased GDM risk, though findings remain inconsistent. Variations in study design, sample types, timing of measurements, and geographical regions contribute to discrepancies. Future studies should focus on critical exposure windows, metabolite specificity, sex differences, and potential confounders to better clarify the relationship between PAE exposure and GDM risk.

Experimental studies and possible mechanisms

PAEs may influence key factors involved in GDM pathogenesis. For instance, tumor necrosis factor- α (TNF- α) plays a significant role in GDM development by promoting adipocyte lipolysis, reducing insulin sensitivity in peripheral tissues, and serving as a biomarker for IR during pregnancy^[63].

To date, only one animal study has directly investigated the link between PAE exposure and GDM. In this study, Sprague-Dawley rats were exposed to a combination of DBP and streptozotocin, resulting in a physiologically relevant GDM model^[78]. In both *in vitro* and *in vivo* studies, DBP exposure was found to downregulate the expression of FoxM1 via the phosphorylation of STAT1 (pSTAT1)^[78]. This molecular alteration led to decreased β -cell viability and increased apoptosis, contributing to the development of GDM^[78].

In summary, PAEs may promote GDM by interfering with inflammatory and transcriptional pathways, particularly through the TNF- α -pSTAT1-FoxM1 axis, which disrupts β -cell survival and insulin regulation.

BISPHENOLS

Bisphenol A (BPA) and its structural analogues, including bisphenol S (BPS), bisphenol F (BPF), bisphenol B (BPB), and tetrabromobisphenol A (TBBPA), are synthetically produced chemicals widely used in the manufacture of polycarbonate plastics and epoxy resins^[79]. Due to their extensive application in consumer products such as food containers, baby bottles, thermal papers, and medical devices, bisphenols are ubiquitous in the environment and human exposure is virtually unavoidable^[80]. These compounds are known endocrine disruptors and have been implicated in metabolic dysregulation, including disturbances in lipid and glucose homeostasis^[81]. Once absorbed through ingestion, inhalation, or dermal contact, bisphenols can interfere with hormone signaling pathways, raising increasing concerns about their potential role in the development of GDM^[82,83]. In response to regulatory restrictions on BPA, structurally similar substitutes such as BPS and BPF are increasingly used, though their safety remains unclear.

Epidemiological studies

In epidemiological studies investigating the association between bisphenols and GDM, nine studies have examined the relationship between BPA and GDM or glucose metabolism, while four studies have simultaneously assessed BPA and its analogs, such as BPS, BPB, and BPF^[7,8,41,67,84-92]. A cross-sectional study conducted by Hou *et al.* involving 390 pregnant women in China assessed urinary BPA levels during 24-28 weeks of gestation but found no significant association with GDM^[84]. In contrast, a case-control study conducted in the United States by Zhu *et al.* reported a significant positive association between first-trimester BPS exposure and GDM risk^[85]. Moreover, elevated BPA levels were linked to increased GDM susceptibility in non-Asian/Pacific Islander populations^[85]. Similarly, a recent Canadian cohort study identified a positive correlation between second-trimester BPA concentrations and GDM risk, supporting the hypothesis that bisphenols may exert endocrine-disrupting effects during pregnancy^[8].

Despite some inconsistencies, evidence suggests that bisphenol-related GDM risk may vary by exposure timing, ethnicity, and individual susceptibility. As BPA use declines, its analogs are increasingly adopted, though their safety remains unclear, underscoring the need for improved toxicological assessment.

Experimental studies and possible mechanisms

Growing experimental evidence supports the role of bisphenols, especially BPA, as endocrine disruptors involved in GDM pathogenesis. A meta-analysis points out that BPA accumulates in adipose tissue, disrupts adipokine secretion, and induces IR, and it impairs insulin signaling via modulation of potassium channels and promotes β -cell apoptosis through mitochondrial damage^[93]. Perinatal BPA exposure also increases diabetes risk in offspring, potentially mediated by epigenetic mechanisms such as altered DNA methylation, histone modification, and miRNA expression^[93].

Animal studies have shown that gestational BPA exposure leads to postpartum glucose intolerance, IR, and weight gain. These effects are linked to impaired insulin secretion, reduced β -cell mass, downregulation of cyclin D2 and CDK4, and upregulation of cell cycle inhibitors such as p16 and p53^[94]. Interestingly, such effects were absent in non-pregnant females, suggesting that pregnancy is a critical window of susceptibility^[94].

With BPA increasingly replaced by alternatives, attention has turned to compounds such as BPS and BPF. A systematic review of 32 studies (25 *in vitro*, 7 *in vivo*) confirmed that BPS and BPF exhibit endocrine-

disrupting activities similar to BPA, including estrogenic, androgenic, and anti-androgenic effects^[95]. BPS mimics estradiol through membrane signaling pathways, thereby influencing cell proliferation and apoptosis, while both BPS and BPF have been shown to alter organ weights, reproductive function, and enzyme expression, collectively raising concerns that these BPA substitutes may pose hormonal risks comparable to those of BPA^[95].

ORGANOCHLORINE PESTICIDES

Organochlorine pesticides (OCPs) are a class of persistent organic pollutants (POPs) and recognized environmental estrogens^[96]. Representative compounds include dichlorodiphenyltrichloroethane (DDT), its metabolite 1,1-dichloro-2,2-bis (p-chlorophenyl) ethylene (DDE), endosulfan, hexachlorobenzene (HCB), and hexachlorocyclohexane (HCH)^[96,97]. Due to their high lipophilicity, chemical stability, and resistance to degradation, OCPs tend to accumulate in biological tissues and undergo biomagnification through the food chain^[98]. Although most OCPs have been banned or strictly regulated, they are still widely detected in soil, water, and human tissues, particularly in adipose tissue, breast milk, and the placenta^[99]. While several epidemiological studies have explored the association between OCP exposure and GDM, toxicological evidence remains limited.

Epidemiological studies

To date, few studies have explored the association between OCP exposure and GDM, and existing findings remain inconsistent [Table 3]^[9,32,35,59,100,101]. Most prospective cohort studies assess OCP concentrations in maternal serum or plasma and involve diverse populations across multiple countries. For instance, a Danish cohort of 604 pregnant women found a positive association between DDT, DDE levels in serum and breast milk at 34 weeks and GDM risk^[35]. Conversely, a United States-based study reported a negative association between early pregnancy HCB levels and GDM^[9]. Other studies conducted in different populations have reported no significant associations^[32,59,100,101].

Overall, current epidemiological evidence on the relationship between OCP exposure and GDM is inconclusive. The heterogeneity in outcomes, ranging from positive to null or inverse associations, may be influenced by differences in population characteristics, timing and type of sample collection, and specific OCP compounds assessed. These findings suggest that the metabolic impact of OCPs may vary depending on the exposure context and compound-specific properties.

PARABENS

Parabens, or alkyl esters of p-hydroxybenzoic acid, have been widely used as antimicrobial preservatives in pharmaceuticals, cosmetics, and food products since the 1930s^[102]. Although they can be absorbed through the skin and other routes, parabens are rapidly metabolized to p-hydroxybenzoic acid and excreted in urine, resulting in a short biological half-life^[103]. Consequently, their systemic toxicity is generally considered low. However, topical application on damaged skin may induce allergic reactions, and patch testing has shown delayed-type hypersensitivity at high concentrations (5%-15%) in sensitive individuals^[104].

In recent years, the widespread use of parabens in moisturizers, sunscreens, and other personal care products has raised concerns over their potential role as emerging environmental pollutants. Trace levels of methylparaben (MeP), ethylparaben (EtP), and propylparaben (PrP) have been detected in breast milk, though concentrations remain well below the acceptable daily intake thresholds^[105]. Research on parabens and GDM has largely focused on epidemiological studies, with limited toxicological evidence available.

Table 3. Summary of epidemiological evidence on the association between BPA, OCPs, APs, and paraben exposure and GDM

Study type	Year	Biological sample			Population		Findings (GM/Med)	Author
		Analyte	Matrix	Gestational week	Country	Size		
Cross-sectional	2021	BPA	Urine	24-28 weeks of gestation	China	390	No association BPA [0.58 µg/L] ^a	Hou et al. ^[84]
Case-control	2013	BPA	Urine	2nd trimester	USA	94	No association BPA [0.80 vs. 1.67 µg/L] ^{a,c}	Robledo et al. ^[86]
Case-control	2022	BPA	Urine	2nd trimester	USA	301	Negative association between BPA [1.85 vs. 2.58 ng/mL] and GDM ^{a,c}	Chen et al. ^[92]
Case-control	2022	BPA, BPS, BPF	Urine	1st and/or 2nd trimester	USA	333	Positive association between BPS [0.6 vs. 0.4 ng/mL], BPA[non-A/PIs][0.6 vs. 0.5 ng/mL] and GDM in the 1st trimester	Zhu et al. ^[85]
Cohort	2015	BPA	Urine	1st trimester	Canada	1,274	No association BPA [0.9 µg/L] ^{a,c}	Shapiro et al. ^[67]
Cohort	2017	BPA	Urine	1st and/or 2nd trimester	USA	245	No association with blood glucose in 1st trimester BPA [1.39 µg/L] ^{a,c} Positive association with increased blood glucose in the 2nd trimester BPA [1.27 µg/L] ^{a,c}	Chiu et al. ^[87]
Cohort	2017	BPA	Urine	3rd trimester	China	620	Negative association with 2h-PG and GDM BPA [2.72 µg/L] ^{a,c}	Wang et al. ^[88]
Cohort	2018	BPA	Urine	1st and/or 2nd trimester	USA	347	No association BPA [1st:1.3; 2nd: 1.28 µg/L] ^{a,c}	Bellavia et al. ^[89]
Cohort	2018	BPA	Serum	10-17 weeks of gestation	UK	232	No association BPA [1.76 µg/L] ^b	Fisher et al. ^[90]
Cohort	2019	BPA, BPS, BPF, BPAF	Urine	1st trimester	China	1,841	Positive association between BPAF [0.030 µg/L] and GDM ^{a,c} Positive association between BPAF, BPS [0.36 µg/L] and FPG ^{a,c}	Zhang et al. ^[91]
Cohort	2021	BPA	Serum	16 and 26 weeks of gestation	USA	388	No association BPA [16w 1.9; 26w 1.8 ng/mL] ^a	Vuong et al. ^[41]
Cohort	2024	BPA, BPS	Urine	2nd trimester	Canada	420	Positive association between BPA [1.12 µg/L] and GDM ^a	Soomro et al. ^[8]
Cohort	2024	BPA, BPS	Urine	2nd trimester	USA	298	No association	Peng et al. ^[7]
Cohort	2014	Chlordecone	Plasma	during labor	French	779	No association Chlordecone [0.4 µg/L] ^b	Saunders et al. ^[100]
Cohort	2016	OCPs	Plasma	1st trimester	Canada	1,274	No association	Shapiro et al. ^[32]
Cohort	2016	OCPs	Serum	Before pregnancy	USA	258	No association	Smarr et al. ^[101]
Cohort	2017	HCB, p, p'DDE	Serum	1st trimester	Greece	939	No association between HCB [103.8 vs. 86.5 pg/mL] and p, p'DDE [2067.9 vs. 2,041.1 pg/mL] and GDM ^a	Vafejadi et al. ^[59]
Cohort	2017	DDE, DDT	Serum milk	34 weeks of gestation	Denmark	604	Positive association between OCPs and GDM Serum DDE [0.54 µg/g lipid]; Serum DDT [0.00 µg/g lipid] ^b	Valvi et al. ^[35]
Cohort	2019	OCPs	Plasma	8-13 weeks of gestation	USA	2334	Negative association between HCB [7.4 ng/g lipid] and GDM ^{a,c}	Rahman et al. ^[9]
Cross-sectional	2025	Parabens	Urine	1st and 2nd trimesters	USA	333	Positive associations between PrP, MeP, and EtP and GDM in A/PI	Peterson et al. ^[10]
Cohort	2019	Parabens	Urine	1st and 2nd trimesters	USA	241	Positive associations between BuP [1st: 0.94; 2nd: 1 µg/L] and glucose levels in 1st trimester and 2nd trimester Negative association between PrP [1st:23.2; 2nd: 25.3 µg/L] and glucose levels in 1st trimester ^{a,c}	Bellavia et al. ^[106]
Cohort	2019	Parabens	Urine	Within 3 days before or after delivery	China	696	Nonlinear associations of PrP [0.49 ng/mL] and the summed estrogenic activity of parabens with GDM in the overweight/obese	Li et al. ^[107]

						population ^{a,c}	
Cohort	2019	Parabens	Urine	8-16 weeks of gestation	China	1,087	Positive association between EtP [0.83 vs. 0.53 µg/L] and GDM ^{b,c} Liu et al. ^[108]
Cohort	2024	Parabens	Urine	2nd trimester	USA	298	Lower IGT/GDM prevalence with detectable EtP Peng et al. ^[1]
Cross-sectional	2021	NP, and 2-t-OP	Urine	24-28 weeks of gestation	China	390	Positive association between 2-t-OP [1.80 µg/L] and GDM Negative association between NP [0.57 µg/L] and GDM ^{a,c} Hou et al. ^[1]
Cohort	2024	NP, 4-n-NP, 4-t-OP, 4-n-OP	Serum	1st trimester	China	2,035	Positive association between NP [107.1 ng/mL] and GDM; Positive association between 4-t-OP [45.91 ng/mL] and GDM in women with female fetuses U-shaped nonlinear association between 4-n-OP [0.92 ng/mL] and 4-n-NP [1.77 ng/mL] with GDM in women with female fetuses ^b Pang et al. ^[1]

^aConcentrations reported as geometric means (GMs). ^bConcentrations reported as medians (Med). ^cConcentrations of BPA, OCPs, Paraben metabolites were SG-adjusted (specific gravity-adjusted) to account for variations in urine dilution, ensuring comparable exposure estimates. BPA: Bisphenol A; OCP: organochlorine pesticide; A/PI: Asian/Pacific islander population; GDM: gestational diabetes mellitus; GM: geometric mean; Med: median; BPS: bisphenol S; BPAF: bisphenol AF; FPG: fasting plasma glucose; 2h-PG: 2-hour plasma glucose; HCB: hexachlorobenzene; p, p'-DDE: dichlorodiphenyldichloroethylene; DDE: dichlorodiphenyldichloroethylene; DDT: dichlorodiphenyltrichloroethane; PrP: propylparaben; MeP: methylparaben; EtP: ethylparaben; BuP: butylparaben; NP: nonylphenol; 2-t-OP: 2-tert-octylphenol; 4-t-OP: 4-tert-octylphenol; 4-n-OP: 4-nonylphenol; 4-n-NP: 4-nonylphenol; IGT: impaired glucose tolerance.

Epidemiological studies

Epidemiological studies examining the association between paraben exposure and GDM are primarily concentrated in the United States and China, with most adopting prospective cohort designs and analyzing urinary biomarkers during pregnancy. To date, findings consistently suggest that paraben exposure is mostly positively associated with GDM risk [Table 3]^[7,10,106-108].

For example, a United States cross-sectional study assessed urinary concentrations of PrP, MeP, and EtP during the first and second trimesters, revealing significant positive associations with GDM, particularly among Asian/Pacific Islander women^[10]. Similarly, a Chinese cohort study by Li *et al.* measured urinary paraben levels near delivery in 696 pregnant women and observed nonlinear associations between PrP and the combined estrogenic activity of paraben with GDM risk, especially in overweight or obese individuals^[107].

Overall, evidence points toward a potentially elevated susceptibility to paraben-related GDM among specific subgroups, with maternal body weight and ethnicity acting as possible effect modifiers. Moreover, the observed non-linear relationships underscore the need to consider complex dose-response dynamics in future studies.

ALKYLPHENOLS

Alkylphenols, including nonylphenol (NP) and octylphenol (OP), are synthetic phenolic compounds with known endocrine-disrupting properties due to their structural similarity to estrogens^[109]. They are commonly used as precursors or degradation products of alkylphenol ethoxylates, which serve as surfactants in industrial applications such as detergents, lubricants, pesticides, plastic additives, and textile processing^[109,110]. Due to their widespread use, environmental persistence, and bioaccumulative potential, alkylphenols have been detected in water, soil, and biological matrices, with human exposure occurring via ingestion, inhalation, and dermal absorption^[111].

Epidemiological studies

To date, only two epidemiological studies have examined the association between alkylphenol exposure and GDM, both conducted in China^[11,84]. Hou *et al.* analyzed urinary concentrations of NP and 2-*t*-octylphenol (2-*t*-OP) in 390 pregnant women during the second trimester, identifying a positive association between 2-*t*-OP and GDM risk, while NP was inversely associated^[84]. A larger cohort study of 2,035 pregnant women assessed multiple NP and OP homologs in early pregnancy serum and found that NP exposure was positively associated with GDM^[11]. Furthermore, high exposure to 4-*tert*-Octylphenol significantly increased GDM risk, particularly among women carrying female fetuses^[11].

These findings, although limited, suggest that alkylphenols may influence GDM risk in a compound-specific and potentially sex-dependent manner. However, the small number and geographic concentration of studies highlight the need for broader, multicenter investigations with more refined exposure assessments.

Experimental studies and possible mechanisms

Mechanistic studies specifically addressing alkylphenols and GDM remain scarce. However, research on T2DM and glucose metabolism offers relevant insights. For instance, in diabetic mice, exposure to xenoestrogens such as BPA and OP improved glycemic control and restored insulin secretion by upregulating β -cell transcription factors (Pdx1, Mafa, Neurod1), potentially via the NF- κ B pathway^[112]. These compounds also modulated hepatic gluconeogenesis, indicating broader metabolic effects.

Prenatal exposure to NP has been shown to induce hyperglycemia, increased body weight, and pancreatic inflammation in male offspring^[113]. Mechanistically, NP disrupted the expression of glucose metabolism-related genes (e.g., *GCK*) and increased mitochondrial uncoupling protein UCP-2, suggesting interference with β -cell development and insulin synthesis^[113].

Collectively, these studies implicate alkylphenols in multiple pathways relevant to glucose dysregulation, yet their specific contribution to GDM remains unclear. More targeted *in vivo* and *in vitro* research is needed to elucidate how alkylphenols influence gestational metabolic adaptation and disease susceptibility.

DISCUSSION

ECs are increasingly recognized as potential environmental risk factors for GDM. Although traditional risk factors for GDM include diet, obesity, and genetics, growing evidence suggests that prenatal exposure to ECs may also impair maternal glucose regulation. This review systematically integrates epidemiological studies on seven major classes of ECs, providing tabular summaries of the associations between different contaminants and GDM for direct comparison. In addition, the review synthesizes available evidence on potential mechanisms [Table 4], including inflammatory responses, oxidative stress, impaired insulin signaling, and gut microbiota dysbiosis, offering insights into the underlying pathways through which ECs may affect glucose metabolism.

Although the potential relationship between ECs and GDM has been systematically summarized, several limitations remain. First, most existing studies have methodological constraints, as they are predominantly cross-sectional or case-control in design, limiting causal inference. Longitudinal studies can better clarify temporal sequences between exposure and outcomes and support causal interpretations; however, they are costly, time-consuming, prone to loss to follow-up, and some only assess exposure at a single time point, which may fail to capture dynamic exposure levels across different stages of pregnancy. Second, exposure assessment methods remain insufficient. Most studies rely on single-point measurements in serum or urine, which may underestimate or overlook long-term low-dose and mixed exposures. In addition, variations in

Table 4. Mechanistic overview of seven classes of ECs on GDM

Mechanism	PFAS	PCBs	PAEs	Bisphenols	OCPs	Parabens	Alkyphenols
β -cell damage or insulin secretion decrease	●	○	●	●	○	○	●
Insulin resistance or tissue metabolism abnormality	●	●	●	●	○	○	●
Inflammation or oxidative stress	●	○	●	●	○	○	●
Nuclear receptor or signaling disruption	●	○	●	●	○	●	●
Developmental or early-life exposure	●	●	○	●	○	○	●

● direct mechanistic evidence; ○ indirect/predicted. EC: Emerging contaminant; GDM: gestational diabetes mellitus; PFAS: per- and polyfluoroalkyl substances; PCB: polychlorinated biphenyl; PAE: phthalate; OCP: organochlorine pesticide.

exposure assessment methods, timing of measurement, and choice of outcome indicators, along with differences in GDM diagnostic criteria, reduce the comparability and consistency of findings across studies. While some studies suggest that ECs may influence GDM through inflammation, oxidative stress, impaired insulin signaling, and gut microbiota alterations, mechanistic evidence for certain contaminant classes remains scarce. For example, parabens and organochlorine pesticides have limited experimental verification, with few systematic *in vitro*, *in vivo*, or animal model studies. Finally, there is substantial heterogeneity across studies. This heterogeneity may arise from differences in population genetics, dietary patterns, lifestyle, and environmental exposure profiles; variations in study design, sample size, exposure assessment methods, and confounding control; differences in contaminant levels and sources across regions; and inconsistent GDM diagnostic criteria. These factors likely influence the stability and comparability of results and partly explain inconsistencies among current findings.

In summary, existing evidence has limitations in study design, exposure assessment, mechanistic exploration, and result consistency. These gaps need to be addressed in future research. First, most current studies focus on a single contaminant or a single class of contaminants, whereas humans are generally exposed to mixtures of pollutants. Differences in sample types suitable for assessing different contaminants further complicate the situation. Therefore, future studies should strengthen research on mixed exposures, develop more comprehensive, precise, and efficient detection methods, and standardize exposure and outcome assessment protocols. Machine learning approaches, such as high-dimensional mixture models, could be applied to simulate real-world human exposures and further evaluate associated health risks. Second, at present, research on the effects of ECs on GDM is largely epidemiological, with relatively few studies based on animal models or *in vitro/in vivo* experiments. Future investigations could utilize the Adverse Outcome Pathway (AOP) framework^[114] or network toxicology^[115] to conduct risk assessments, integrate mechanistic information across different contaminants, and strengthen bidirectional validation between mechanistic and epidemiological evidence to improve the systematic understanding of pathogenic mechanisms.

In addition to the seven major classes of ECs summarized in this review, microplastics and pharmaceutical residues, which are more closely related to daily human life, also deserve attention. Microplastics are commonly present in the environment and may enter the human body through various pathways, such as drinking water, food, and air^[116]. Evidence suggests that microplastics can induce inflammatory responses, oxidative stress, and gut microbiota dysbiosis, all of which may be closely linked to glucose metabolism disorders and GDM development^[117,118]. Moreover, microplastics may serve as carriers for other toxic substances, potentially amplifying their effects^[119]. However, evidence on the metabolic impacts of microplastics on pregnant populations remains limited, and future studies should combine epidemiological investigations with mechanistic research for deeper insights. Pharmaceutical residues primarily originate from improper use of antibiotics, hormones, and other drugs in daily life or from environmental

contamination and can enter the human body via food, water, or environmental exposure^[120]. Some residues possess endocrine-disrupting properties, potentially affecting glucose metabolism and insulin sensitivity directly or indirectly^[121]. Given the regional variability of pharmaceutical residues, future research should clarify the risks associated with long-term low-dose exposure in pregnant women and fetuses and consider local dietary and environmental characteristics to inform food safety and public health policies.

CONCLUSION

ECs are increasingly recognized as potential environmental risk factors for GDM. While traditional contributors to GDM include diet, obesity, and genetics, growing evidence suggests that prenatal EC exposure may also impair maternal glucose regulation. However, current research remains limited in both epidemiological scope and mechanistic understanding. This review summarizes the associations between seven major classes of ECs and GDM, highlighting several key gaps: inconsistent findings across studies, limited temporal resolution of exposure assessments, and insufficient investigation of mixture effects. Mechanistic studies suggest that ECs may disrupt insulin signaling, induce oxidative stress, and impair β -cell function, yet such evidence is still lacking for some compounds such as parabens and organochlorine pesticides.

DECLARATIONS

Authors' contributions

Study design: Li, H.; Wei, Y.; Peng, Y.

Data collection and analysis: Wei, Y.; Liu, M.; Wang, W.; Zou, X.

Data interpretation and manuscript preparation: Wei, Y.; Zhu, Z.; Zou, X.; Li, H.; Liu, M.; Peng, Y.

All authors reviewed and approved the final manuscript.

Availability of data and materials

Access to the trial data is restricted due to signed consent agreements on data sharing, which permit use only by external researchers conducting studies aligned with the objectives of this project. Researchers who wish to obtain the data used in this study can submit a request to the corresponding author.

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Conflicts of interest

Han Li is a Junior Editorial Board member of *Journal of Environmental Exposure Assessment*. Han Li was not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, or decision making. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Declaration of generative AI use

During the preparation of this work, the authors used ChatGPT to improve language expression and check grammar. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

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