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Endocrine Disruptors in Pregnancy: Effect on Mother and Fetus - A Review

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Endocrine Disruptors in Pregnancy: Effect on Mother and Fetus—A Review

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Abstract: Background/Objectives: Endocrine disruptors are ubiquitous agents in the environment and are present in everyday consumer products. These agents can interfere with the endocrine system, and subsequently the reproductive system, especially in pregnancy. Increasing research has been conducted to discover and describe the health effects of these agents on humans, including pregnant women, their fetuses, and the placenta. This review discusses prenatal exposure to various endocrine disruptors focusing on Bisphenols, Phthalates, Organophosphates, and Perfluoroalkyl substances, and their effects on pregnancy and fetal development. **Methods**: We reviewed the literature via PubMed and EBSCO databases and included the most relevant studies. **Results**: Our findings reveal that several negative health outcomes were linked to endocrine disruptors. However, despite the seriousness of this topic and the abundance of research on these agents, it remains challenging to draw strong conclusions about their effects from the available studies. This does not allow for strong, universal guidelines and might result in poor patient counseling and heterogeneous approaches to regulating endocrine disruptors. **Conclusion**: The urgency of the matter calls for urgent efforts, as more studies are needed in this realm, to protect pregnant patients ultimately and in the long term, society.

Keywords: endocrine disruptors; bisphenol A; phthalic acids; organophosphates; fluorocarbons; environmental exposure; pregnancy; fetal development

1. Introduction

The World Health Organization (WHO) defines an endocrine disruptor (ED) as "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations." [1] These agents, both natural and manufactured, are ubiquitous in the environment and can be found in numerous everyday consumer products [1–3]. Exposure can also occur through contaminated food, contaminated groundwater, and combustion sources [1].

EDs often enter the environment via agricultural and industrial practices [2,3]. For instance, agricultural EDs include phytoestrogens, persistent organic pollutants (POPs), and herbicide

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glyphosate. While phytoestrogens (daidzein, and genistein) are naturally found in soybeans and other legumes, POPs such as dichlorodiphenyltrichloroethane (DDT), and the metabolite dichlorodiphenyldichloroethylene (DDE), are synthetic EDs and exposure sources include pesticides, waste burning, and paper bleaching [2,3]. Bisphenols including bisphenol A (BPA), bisphenol S (BPS), bisphenol F, and bisphenol AF (BPAF), and high molecular weight phthalates, such as bis (2-ethylhexyl) phthalate (DEHP) and its metabolite mono-2-ethylhexyl phthalate (MEHP), are often used in plastics, food packaging, and dental sealants [2,3], while low molecular weight phthalates are often used in cosmetics and personal hygiene products [3]. Polycyclic aromatic hydrocarbons include polybrominated diphenylethers (PBDEs) and polychlorinated biphenyls (PCBs) and are commonly used in electronics furniture, hydraulic fluids, and flame retardants for the insulation of electrical installations [2,3]. Parabens are used as preservatives in cosmetics [2], and, finally, PFAS are synthetic EDs found in polishes and paints as well as non-stick cookware [3].

The human endocrine system is quite complex in its interaction with multiple organ systems, especially the reproductive system. EDs can interfere with these interactions and lead to endocrine system dysregulation. The developmental origin of health and disease theory, i.e. "Barker hypothesis" as pioneered by epidemiologist Dr. David Barker, suggests a link between adult metabolic disorders and the preconceptual, fetal, and early infant phases of life [4]. This ground-breaking theory suggested that diet, lifestyle, and environmental insults can impact the maternal-fetal-placental unit and ultimately lead to disease in the adult phase of life. Similarly, it is believed that EDs can induce epigenetic modifications in fetal cells in utero. Some EDs were also described as a leading cause of reproductive disorders, impacting fertility and causing gametes anomalies during fetal development [3]. Pregnancy thus represents a critical period, yet data on this population appears to be scarce. Most studies have focused on accidentally highly exposed groups and external environmental sources of contamination such as air, food, and water rather than internal exposure (blood, tissue) [1], with limited in vivo studies. In addition, most studies on EDs exposure in pregnancy have been divergent, examining different outcomes at different points in time. One study rarely tackles all categories of EDs and all their outcomes in pregnancy.

In light of the growing awareness and concern, stakeholders established regulations and passed legislation to identify and control the use of such agents. Despite the tremendous disease cost due to EDs and the fact that several health, medical, and scientific organizations have released statements on their harmful effects, current regulatory agencies and policies rarely hold manufacturers responsible for the consequences of these agents [5].

The main objective of this review is to create a compilation of all potential EDs encountered in pregnancy and their effects on pregnancy and fetal development, as well as to provide an update on the available research and the limitations that remain. We conducted a thorough literature review using PubMed and EBSCO databases, focusing on the effects of Bisphenols, Phthalates, Organophosphates, and Perfluoroalkyl substances.

2. Mechanism of Action

The prenatal period is a very sensitive window for fetal development. Any perturbation in the maternal endocrine system or placental function can lead to derangement in fetal growth and development. At a molecular level, EDs can alter gene expression by interacting directly with a family of nuclear hormone receptors (NHRs) that function as transcription regulators to either activate or repress gene function. A similar transcription factor that also serves as a target for EDs is the aryl hydrocarbon receptor (AhR), which regulates the expression of several genes including the cytochrome P450 (CYP)-1 gene family members [6]. The biological mechanisms and molecular signaling pathways are quite complex and remain a subject of growing interest and research.

The role of the placenta is vital in pregnancy in that it regulates multiple endocrine, immunological, and physiological processes throughout pregnancy, but it is not always an effective barrier against EDs [6]. EDs including PBDEs, BPA, and PCBs can potentially pass from the mother to the fetus through the placenta and have been detected in the placenta [6,7]. Aside from crossing the placenta, entering fetal circulation, and accumulating in fetal tissue, EDs are also capable of

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disrupting placental growth and function. The susceptibility of the placenta to EDs is largely due to the extensive expression of hormone receptors in the placenta and the ability of EDs to alter the hormonal equilibrium, either by binding to these receptors and hormone transport proteins or by interfering with the degradation and synthesis of endogenous hormones [7]. For instance, PBDE and PAH levels in umbilical cord blood correlate with the expression of IGF-1 and IGFBP-3 mRNA levels in the placenta [8]. Since EDs can alter, mimic, or disrupt the function of gestational hormones, pregnancy remains especially sensitive to their actions [9]. In addition, the lack of placental and fetal enzymes as weaponry against EDs [7] makes the fetus highly vulnerable to any alterations that can disrupt fetoplacental homeostasis. Thus, the effect of EDs on the fetoplacental unit should not be underestimated.

Finally, the uterus can also be affected by exposure to EDs. Studies have shown that certain EDs such as BPA can arrest endothelial proliferation and decrease vascular endothelial growth factor (VEGF) mRNA expression, thus interfering with implantation [2].

3. Common Endocrine Disruptors: Sources and Effects on Pregnancy and Fetal Development

3.1. Bisphenol A

3.1.1. Sources of Exposure

Bisphenols are released mainly from polycarbonates and epoxy resins and include BPA, BPS, bisphenol F, bisphenol M, and BPAF. Bisphenols are often used in food packaging, plastic dinnerware, dental sealants, and thermal receipts [2,3,9]. Notably, over 90% of the overall BPA exposure is thought to be through diet [10], and BPA was banned by the Commission Regulation (EU) from the manufacture of infant feeding bottles in 2011 [11]. While BPA intake was shown to vary from one country to another, pregnant women were noted to have a significantly higher BPA intake than the general population [12]. Several studies have shown that BPA is transported through the placenta and can accumulate in the placental trophoblast and affect placental growth.

3.1.2. Postnatal Endocrinological Outcomes

Several studies have examined the effect of prenatal BPA exposure on the development of diabetes, obesity, and cardiovascular disease in adulthood. Animal studies have been conflicting; some suggested that BPA might have an obesogenic effect while others showed no association between BPA and BMI, with some even showing an inverse correlation between BPA exposure and BMI [13]. The reason behind these discrepancies is unclear but might be explained by differences in methodology of the way BPA is administered, the dose and timing of administration, the type of species involved, and the sample size. It is well known that obesity is a risk factor for diabetes, hence several mechanisms have been proposed to explain how BPA exposure can alter BMI and potentially glucose homeostasis and predisposition to diabetes. It has been suggested that exposure to BPA at different periods of time can affect β-cell pancreatic function and lead to differences in the quantity and quality of β-cells, ultimately leading to decreased insulin production. In addition, insulin resistance also occurs, leading to increased adiposity and decreased glucose tolerance [14]. In vitro and in vivo studies have shown that BPA exposure can induce adipogenesis and triglyceride accumulation in mice and inhibit the release of adiponectin, a hormone present in adipocytes that is believed to protect against insulin resistance and metabolic syndrome [15].

Very few studies exist on BPA exposures in humans and care must be taken when extrapolating from animal studies due to the developmental difference between species [14]. For example, pancreatic development in rodents occurs both in the prenatal and postnatal period, whereas in humans the bulk of the development occurs in the prenatal period. When looking at human data, several studies have shown an association between BPA exposure in childhood and adulthood, and obesity [16]. However, most of these studies have been cross-sectional and did not focus on the prenatal window of exposure. Only three studies (two US cohorts and one European cohort) attempted to evaluate BPA exposure in utero by measuring maternal creatinine-adjusted urinary

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BPA concentrations and childhood-related obesity outcomes [13,15,16]. Both the California and Cincinnati cohorts found that contrary to animal studies, prenatal BPA exposure in humans was not associated with significant changes in BMI. In fact, both cohorts found that a high maternal urinary BPA was associated with a lower BMI in childhood amongst girls; however, the association was not significant. On the other hand, the Spanish cohort found that maternal urinary BPA concentrations during pregnancy were associated with increased child BMI and waist circumference, manifesting at four years of age. Differences in outcomes between the three different cohorts could be due to confounding and misclassification of BPA exposure, as well as selection bias.

The effect of maternal exposure to BPA during pregnancy on fetal thyroid function has been investigated in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study, and an inverse association was found between maternal BPA concentration and total T4 levels, but not free T4, specifically in male offspring. The association appears to be stronger in the third trimester, which may suggest either a transient effect or alternatively a window of susceptibility and concern [17].

The CHAMACOS cohort was also used to study the effects of phthalates and BPA on pubertal development and revealed that high-molecular-weight phthalates and BPA were associated with later puberty in girls and earlier puberty in boys [18].

The Infant Development and the Environment Study (TIDES) is another cohort study designed to evaluate the effect of BPA on the reproductive development of female offspring by using the anogenital distance as a biomarker of the fetal hormonal milieu and a measure of reproductive toxicity. The investigators concluded that higher first-trimester BPA exposure was associated with significantly shorter anogenital distance in daughters, suggesting that BPA indeed may impact reproductive development [19].

3.1.3. Postnatal Cardiovascular Outcomes

The effect of bisphenols on vascular modulation and its effect on the cardiovascular system has also been a subject of interest. In a recent prospective cohort study of 935 mother-child pairs, Blaauwendraad et al. hypothesized that maternal exposure to bisphenols during different trimesters of pregnancy can affect fetal vasculature and impair arterial health [20]. However, a higher maternal urinary total bisphenol, specifically BPA concentrations, was associated with lower carotid intima-media thickness. This was contradictory to prior studies that have shown a positive correlation between higher exposure to BPA and carotid intima-media thickness. Notably, these studies were conducted in adults exposed to bisphenols, whereas Blaauwendraad et al.'s study is the only study to date conducted in offspring exposed to bisphenol prenatally. The discrepancy in the results could be explained by the differences in pathophysiology in the two populations: In adults, exposure to BPA seems to increase oxidative stress, which is known to accelerate the formation of atherosclerotic plaques; whereas, in the fetal period, exposure could cause structural vascular adaptations rather than development of plaques. The significance of a thinner carotid intima-media thickness is still unclear and whether or not this could lead to a weaker, more "vulnerable" vasculature remains under question.

3.1.4. Postnatal Neurological Outcomes

The neurodevelopmental and behavioral effects of BPA exposure in utero have been a subject of growing interest. Grohs et al. examined the effect of prenatal BPA exposure on brain microstructure in 98 mother-child pairs from the Alberta Pregnancy Outcomes and Nutrition (APrON) study in Canada [21]. The investigators found an association between maternal urinary BPA concentrations during the second trimester and poor development of the splenium and in the right inferior longitudinal fasciculus, suggesting that prenatal exposure to higher BPA doses during the second trimester may result in less developed white matter in the inferior and posterior brain regions, as compared to children exposed to lower BPA doses. Interestingly, no association was found between postnatal urinary BPA and white matter development, suggesting that prenatal rather than postnatal BPA exposure may shape and organize brain development. Similar studies have supported this

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finding; however, this study was unique in the fact that the investigators used the MRI as a quantitative effect biomarker.

Numerous studies support the notion that early BPA exposure can have an impact on childhood internalizing and externalizing behavior. Braun et al. concluded that maternal urinary BPA concentration during pregnancy was associated with some aspects of children's behaviors at three years of age, specifically, poorer reciprocal social behaviors among all children, more internalizing and somatization behaviors in boys, and poorer working memory and planning/organizing abilities in boys [22]. Similarly, the Odense child cohort revealed that prenatal BPA exposure even in low concentrations may increase the risk of Autism Spectrum Disorder (ASD) symptoms, which may predict later social abilities [23].

3.1.5. Pregnancy Loss

After a thorough review of the literature, we identified only one study that evaluated the effect of prenatal BPA exposure on the luteal phase and miscarriage. BPA was found to be associated with a shorter luteal phase but not associated with an increased time to pregnancy or early pregnancy loss. These findings are of particular interest because the samples were collected from 221 healthy women during a period (1982–1986) where BPA exposure was generally higher than it is nowadays [24].

3.1.6. Preeclampsia

Two case-control studies found an association between maternal BPA concentration and preeclampsia [25,26]. The case-control lead by Leclerc noted BPA accumulation in the placenta of preeclamptic women, but not the umbilical cord or peripheral maternal blood, suggesting that the UGT pathway, which is the main pathway for BPA metabolism, is altered more selectively in the placenta that in the liver of preeclamptic women, leading to BPA accumulation in the placenta rather than peripheral blood [25]. The research group also suggested that BPA is believed to alter angiogenesis by impairing estrogen production through downregulation of aromatase activity, thus leading to preeclampsia and other complications. Other researchers have also suggested that elevated BPA concentrations can induce apoptosis of trophoblastic cells, which could explain the pathophysiology of preeclampsia. These studies have paved the way to further investigate the link between BPA metabolism and preeclampsia.

3.1.7. Preterm Birth

Two nested case-control studies, one in Boston and the other in Mexico City, attempted to evaluate the effect of prenatal maternal BPA exposure and preterm birth [27,28]. The Mexico City study group found an OR=2.5 of having a preterm birth in relation to third trimester BPA concentration [28]. The Boston study group was not found to have a significant association between BPA concentration and preterm birth. However, when the investigators further stratified the results by type of preterm birth (spontaneous preterm birth, defined by the investigators as preterm birth resulting from preterm labor or premature rupture of membranes, vs. placental etiology) and neonatal sex. They found a significant association between BPA levels in the third trimester and high rates of spontaneous preterm birth of female infants specifically [27]. These findings could be explained by the fact that BPA has been found to stimulate the production of pro-inflammatory cytokines, which could initiate an inflammatory cascade, to which female infants appear to be more susceptible. This inflammatory cascade then leads to preterm labor or rupture of membranes. Interestingly, there was no association found between BPA concentration and preterm delivery due to placental etiology (growth restriction, preeclampsia), despite prior proposed mechanisms of BPA-induced trophoblastic apoptosis and impairment of estrogen-mediated angiogenesis. Given the scarcity of data, these results should be interpreted with caution.

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3.1.8. Fetal Growth

Several nested case-control and cohort studies attempted to investigate the effect of BPA exposure on fetal growth; however, results have been inconsistent. Snjider et al. studied a cohort of 219 Dutch women and found that women exposed to higher levels of BPA had lower growth rates for fetal weight and head circumference [29]. Another nested case-control study from China also concluded that urinary BPA concentrations in the third trimester were associated with an increased risk of low birth weight [30]. In contrast, a study from South Korea [31] and a French cohort found a positive association between maternal BPA concentration and fetal head circumference [32]. Several studies from the US and Spain did not report a significant association between BPA exposure and fetal growth [33,34].

The discrepancies in the results between different studies can have several reasons. For example, despite that the aforementioned studies measured BPA in urine, their sample collections can vary. While some investigators collected one spot urine sample from each participant, others collected more samples throughout different pregnancy trimesters. In addition, a lack of assessment of other confounding endocrine disruptors in some studies might also affect the outcome.

3.2. Phthalates

3.2.1. Sources of Exposure

Phthalates are chemicals that are often referred to as "plasticizers." and are present in everyday products [35,36]. High molecular weight phthalates are often used to synthesize flexible plastic used in food storage containers, medical equipment, and flooring, and exposure to them is often through ingestion, whereas low molecular weight phthalates are often used in personal care items (shampoos, lotions, and fragrances), with exposure usually occurring through dermal absorption or inhalation [35].

3.2.2. Preterm Birth

In a recent systematic review and meta-analysis, Wang et al. included seven studies investigating the association between phthalates and preterm birth and found a positive association for several metabolites including mono-n-butyl phthalate (MBP), sum of di-2-ethylhexyl phthalate (ΣDEHP), and mono 3-carboxypropyl phthalate (MCPP) [37]. A limitation of this meta-analysis is the lack of stratification of phthalate exposure by trimester. However, current data from several cohorts including Furgeson's PROTECT cohort [38], Boston cohort [39], and the MIREC study pan-Canadian cohort [40] suggests that the relationship between preterm birth and phthalate exposure is dose-dependent and strongest in later gestation, particularly in the late second trimester and third trimester. Very few studies have stratified the outcomes of prenatal phthalate exposure by fetal sex. In a recent study, Cathy et al. utilized the PROTECT cohort to further explore differences in these associations based on fetal sex and found a stronger selection for monoisobutyl phthalate (MiBP) and monohydroxyisobutyl phthalate (MHiBP) and monocarboxynonyl phthalate (MCNP) with spontaneous preterm birth, among women carrying a male compared to a stronger selection of MBP and monohydroxybutyl phthalate (MHBP) for preterm birth, for mothers carrying a female fetus [35]. Several studies have demonstrated an increase in biomarkers of oxidative stress and inflammation in women exposed to phthalates, which explains the early initiation of labor in these women [41,42].

3.2.3. Preeclampsia

A recent systematic review and meta-analysis included 10 human epidemiological studies to investigate the relationship between phthalate exposure and blood pressure changes in pregnancy. The findings suggest that several metabolites including MBP, monobenzyl phthalate (MBzP), and MEHP are associated with blood pressure changes in pregnancy; and monoethyl phthalate (MEP) in particular was associated with hypertensive disorders of pregnancy [43]. Data from the Health Outcomes and Measures of the Environment Study (HOME) suggests that maternal urinary MBzP

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concentrations may be associated with increased diastolic blood pressure and risk of pregnancy-induced hypertensive diseases [44]. The effects of phthalates on blood pressure appear to extend to the postpartum period. Women participating in the Programming Research in Obesity, Growth, Environment, and Social Stressors (PROGRESS) longitudinal study were found to have elevated blood pressures up to 72 months postpartum [45].

While several pathways have been proposed to explain the effects of phthalates on blood pressure, the exact mechanism remains uncertain [43]. One proposed pathway is the renin-angiotensin-aldosterone system, which can be inhibited by phthalates. Multiple studies have also shown that phthalates can increase oxidative stress, which ultimately leads to an increase in circulating angiogenic factors linked to hypertensive disorders in pregnancy. More studies are emerging on the effects of phthalates on maternal thyroid function and how that could potentially indirectly impact blood pressure through pregnancy.

3.2.4. Gestational Diabetes

In a recent systematic review, phthalate exposure during pregnancy was associated with poor glycemic controls. In addition, three out of 5 human studies revealed a positive association between several phthalates and gestational diabetes mellitus [46].

3.2.5. Thyroid Function

Several epidemiological studies investigated the effect of phthalates on maternal thyroid function and demonstrated that some phthalate metabolites can potentially alter maternal thyroid function; however, the direction and magnitude of this effect are still uncertain. Huang et al. observed a significant association between phthalates and plasma-free and total T4. In contrast, other studies showed no association between phthalate metabolites and free and total T4 [47]. These results also conflict in comparison to studies done in non-pregnant women and adult men. Kuo et al. and Johns et al. both report an inverse association between phthalate metabolites and TSH [48,49]. These studies have not assessed the level of thyroid antibodies.

During the first trimester, the fetus relies exclusively on maternal thyroid function, and any alteration in maternal thyroid function can potentially affect the fetus negatively. Several mechanisms have been proposed to explain how phthalates can potentially alter maternal thyroid function by affecting the hypothalamic-pituitary-thyroid axis and/or interfering with thyroid biosynthesis and biotransport, peripheral conversion, as well as receptor function [48].

3.2.6. Fetal Growth

Studies have been inconsistent regarding the effects of phthalate and fetal growth restriction or low birth weight. Inconsistencies appear to arise from the heterogeneity of these studies and limitations that arise when comparing the effect of different single phthalates to phthalate mixtures. Data suggests that the effect of phthalates on birth weight may be skewed by gender and/or gestational age at the time; however, more data is needed. A recent study on a cohort in Wuhan, China revealed trimester-specific and sex-specific effects of prenatal exposure to DEHP and its metabolites. For example, the study revealed significant negative relationships between maternal urinary DEHP levels and fetal growth, and significant positive associations of some DEHP metabolites with average postnatal weight and BMI z-scores, among male offspring. While some DEHP metabolites during the third trimester were significantly related to the weight gain rates from 6 to 12 months of age among boys, DEHP levels during the second trimester were positively related to the weight gain rates at 6, 12, and 24 months old among boys. Among girls, however, a significant negative relationship between DEHP during the first trimester and weight gain rates was reported, while no significant associations between DEHP and its metabolites and weight gain rates at 12 and 24 months were observed. [50]. Another study conducted on a Japanese cohort reported that DEHP exposure causes reduced fetal weight and crown-rump length, in a gender-independent manner [51]. A third study on a cohort from Boston also observed an inverse association between urinary ∑DEHP

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metabolites levels and fetal growth [52]. It is hypothesized that one of the mechanisms that leads to fetal growth restriction is the effect of phthalates on placental weight, which ultimately leads to placental insufficiency and intrauterine growth restriction [53].

3.2.7. Prenatal and Postnatal Neurodevelopmental Outcomes

Several studies have investigated the effects of prenatal and postnatal phthalate exposure on neurocognitive development. Some studies on postnatal phthalate exposure have demonstrated a decline in IQ scores [36,54], while some showed no association between this exposure and psychomotor development [55]. The mechanism explaining the results of the former group of studies remains uncertain, but one proposed mechanism is through the alteration of thyroid function essential to neurodevelopment in utero. Another proposed mechanism is a decrease in the number of midbrain dopaminergic neurons, tyrosine hydroxylase biosynthetic activity, and tyrosine hydroxylase immunoreactivity [36,54]. Studies on prenatal exposure to phthalates on neurocognitive development have remained inconsistent; while some studies found that such exposure was not associated with children's IQ scores [36] or neurodevelopment [56], others showed an inverse relationship between this exposure and a child's motor development [55] and decreases in psychomotor development and with increased odds of psychomotor delay [57].

A few studies including the MARBLES study investigated the effect of prenatal phthalate exposure on autism. In this cohort, using 14 metabolites of eight phthalates in 636 multiple maternal urine samples collected during the 2nd and 3rd trimesters of pregnancy from 201 mother-child pairs and at three years old, children were clinically assessed for ASD. The study concluded that there is no increased risk of ASD in children exposed to phthalate in mid- to late pregnancy [58]. In a more recent prospective cohort study conducted on a Canadian cohort of 2001 pregnant women, the investigators concluded that higher gestational concentrations of some phthalate metabolites in the first trimester were associated with higher scores of autistic traits in boys, but not girls; however, it appears that these effects can be mitigated by folic acid supplementation [59].

3.3. Organophosphates

3.3.1. Sources of Exposure

Organophosphates are often found in pesticides (herbicides, insecticides…), chemical warfare, plastic packaging, flame retardants, and lubricants [60–62]. Exposure is predominantly through dermal absorption or ingestion, and ingestion of crops sprayed with organophosphate pesticides contributes largely to organophosphate poisoning in humans [60]. Accidental intoxication and suicidal attempts with organophosphate pesticides are also a serious concern [61].

3.3.2. Neurodevelopment

It is well known that the primary target of organophosphates is acetylcholinesterase (AChE), which degrades the neurotransmitter acetylcholine. Through poisoning, excess acetylcholine builds up and works on several effector regions, mainly the neuromuscular junctions, skeletal nerve-muscle junctions, central nervous system, and autonomic ganglia [60]. Several studies have focused on organophosphate exposure and neurobehavioral development. In the CHAMACOS study, the investigators describe an inverse relationship between the agricultural use of organophosphate pesticides within 1 km of maternal residences during pregnancy and cognitive development in children at seven years of age [63]. In a Chinese prospective cohort, Wang et al. used the Bayley scale, mental development index (MDI), and psychomotor development index (PDI) to evaluate the effect of prenatal exposure to organophosphate on cognition, language, and social development. The investigators concluded that prenatal exposure to organophosphates especially in the first trimester was associated with lower Bayley scores in children, particularly in boys [64]. A systematic review that included 13 studies from low- to middle-income countries (LMIC), however, found inconsistent associations between pregnancy exposure to organophosphates, pyrethroids, and carbamates and child development up to seven years of age [65]. Similarly, the French PELAGIE cohort and the

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Generation R study found no significant association between IQ scores and prenatal exposure to organophosphates [66,67].

The New York Mount Sinai cohort concluded that prenatal organophosphate metabolites in urine were associated with an increasing number of abnormal primitive reflexes in neonates as evaluated by the Brazelton Neonatal Behavioral Assessment Scale [68]. Similarly, the CHAMACOS cohort in California concluded that prenatal exposure to organophosphates was associated with poorer neonatal reflexes, attention skills, and intellectual development [69]. These findings were also comparable to the Shenyang Chinese cohort, which noted lower Neonatal Behavioral Neurological Assessment (NBNA) in neonates exposed to organophosphate [70].

Several studies have noted an association between organophosphate exposure prenatally and the development of ASD, including the CHARGE study which collected data from mothers who lived within 1.5 km (just under one mile) of an agricultural pesticide application [71] and the CHAMCOS cohort [72]. Schmidt et al. also described the attenuating effect of folic acid supplementation in the first month of pregnancy on ASD in women exposed to organophosphates [73].

3.3.3. Fetal Growth

The largest study to date that investigated the effects of organophosphate and fetal growth was a pooled analysis published by Harley et al., including 1,235 women pooled from the CHAMACOS, HOME, Columbia, and Mount Sinai birth cohorts, with key differences between cohorts including enrollment years, gestational age at which urine samples were collected, the number of urine samples collected, and the race/ethnic composition of the studied population. The investigators correlated prenatal exposure among black women with decreased infant size at birth but found no evidence of lower birth weight, length, or head circumference among whites or Hispanics [74]. The second largest study conducted on a cohort of 858 women from Denmark did not find an association between organophosphate exposure measured at 28 weeks of gestation and birth weight, length, or abdominal or head circumference at delivery [75]. Finally, the third largest study was conducted on the Generation R Rotterdam cohort and found that organophosphate exposure was associated with decreased fetal weight and length measured during mid-pregnancy, but not at delivery [76].

3.4. Perfluoroalkyl Substances

3.4.1. Sources of Exposure

Perfluoroalkyl substances (PFAS) are commonly found in non-stick cookware, food packaging, shampoos, lubricants, and carpets [77–79]. These substances pass the food chain through the ingestion of contaminated food and beverages, which represents the main way of direct exposure to PFAS [79]. This large group of chemicals includes perfluoroalkyl carboxylic acids (PFCAs), perfluorooctanoic acid (PFOA), perfluoroalkyl sulfonic acids (PFSAs), perfluorohexane sulfonic acid (PFHxS), and perfluorooctane sulfonate (PFOS) [77,79]. Not only are PFAS ubiquitous, but they are also extremely stable and most of them are resistant to degradation, resulting in increasing accumulation in the environment [77–79].

3.4.2. Miscarriage

In a case-control study, strongly significant associations were reported between serum concentrations of PFAS (perfluorodecanoic acid (PFDA) and especially, perfluorononanoic acid (PFNA)) and miscarriage, and almost significant association with PFHxS exposure, while several studies reported no consistent link to miscarriage and stillbirths in a population with high PFOA exposure [79].

3.4.3. Thyroid Function

A recent systematic review included a total of 12 studies assessing the effect of prenatal exposure to PFAS on thyroid function [80], aiming to determine whether a link exists between PFAS exposure

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prenatally, thyroid function, and ASD. In this review, Shin et al. hypothesized that thyroid dysfunction following PFAS exposure can affect fetal brain development. One out of the 12 studies found no association between PFAS exposure and thyroid dysfunction. The rest of the studies showed altered thyroid hormone levels in either maternal blood or the umbilical cord after PFAS exposure. The direction and the magnitude of the association remain inconsistent throughout the studies. In addition, most of the studies included in the review failed to measure important biomarkers that might affect maternal thyroid function, such as iodine status or thyroid antibodies [80].

3.4.4. Obesity

Three recent meta-analyses evaluated the effects of prenatal PFAS exposure and the development of childhood obesity. Fragione et al. concluded that prenatal PFAS (except for PFHxS) exposure may increase the risk of childhood obesity, as measured by BMI; however, these findings were not statistically significant [81]. These findings echoed those of Stratakis et al., who found similar positive but non-statistically significant associations [82]. Similarly, Frigerio et al.'s comprehensive systematic review suggests mostly positive possible associations between prenatal exposure to some PFASs and childhood BMI [83].

One proposed mechanism by which PFAS appears to alter childhood adiposity is via activation of PPARα signaling pathways, involved in modulating lipid and glucose metabolism, and the differentiation of adipocytes. Another proposed mechanism is via alteration of the hypothalamic-pituitary-thyroid axis [81].

3.4.5. Fetal Growth

Several studies have suggested an association between PFAS exposure and low birth weight. In their meta-analysis, Gui et al. included 46 studies and concluded that certain types of PFAS are increasingly proven to partly reduce physical measures such as birth weight, birth length, and head circumference, and increase the incidence of adverse birth outcomes such as preterm birth, low birth weight, and small for gestational age [84].

The modulating effects of folate supplementation on the association between PFAS and fetal growth have also been a subject of interest. In a recent prospective prebirth cohort study that included 1,400 mother-singleton pairs, Zhang et al. concluded that higher early pregnancy PFAS concentrations were associated with lower birth weight only among mothers whose early pregnancy dietary folate intake or plasma folate levels were below the 25th percentile [85].

3.4.6. Neurobehavioral Disorders

Several studies have been published on the association between prenatal PFAS exposure and neurobehavioral disorders, particularly attention deficit disorders (ADHD), autism, and behavioral disorders. The results of these studies remain inconclusive. Forns et al. included nine European population-based studies encompassing over 4,826 mother-child pairs and concluded there was no increased prevalence of ADHD in association with either exposure PFOS or PFOA. However, the stratified analyses of this study suggest that there may be an increased prevalence of ADHD in association with PFAS exposure in girls, children from nulliparous women, and children from low-educated mothers. Studies included in this meta-analysis did not exclusively focus on prenatal exposure to PFOS and PFOA but also included studies with concentrations of PFOS and PFOA measured in maternal serum/plasma during pregnancy, or in breast milk, with different timing of sample collection in each cohort [86].

In a recent meta-analysis focused exclusively on prenatal exposure to PFAS and including 11 studies encompassing 8,493 participants, Yao et al. concluded that PFOA and PFOS exposure during pregnancy might be associated with ADHD in offspring, while prenatal PFOS and PFNA exposure might be associated with ASD in offspring [87]. In the PELAGIE mother-child cohort, prenatal exposure to nine PFAS was measured from concentrations in cord serum samples and behavior was

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assessed at age 12 years in 444 children. The investigators' findings suggest that PFAS exposure prenatally is not only associated with externalizing behaviors but also with internalizing behaviors such as general anxiety and major depressive disorder [88].

4. Prevention

The past few years have witnessed a recent increase in the number of animal and human studies that investigated the effects of prenatal exposure to EDs on maternal and fetal health. Despite the abundance of research available on the topic, results remain heterogeneous and difficult to interpret and draw precise causal-effect conclusions. Studies also remain insufficiently powered to detect significant results. Challenges faced in research include difficulty in quantifying exposure, comparing single compounds vs. mixtures of compounds, differentiating exposure by pregnancy trimester, and assessing longitudinal outcomes to account for the lag time between exposure and manifestation of disease while still accounting for potential confounders. Exploring the epigenetic and dose-related effects of ED exposure adds to the complexity of designing such a precise study and calls for new research designs and more robust techniques.

Despite these limitations and the absence of causal evidence, The Royal College of Obstetricians and Gynecologists stresses the importance of informing mothers of the sources and routes of exposure, the potential harmful fetal and maternal effects, and the importance of minimizing exposure [89]. Also recognizing EDs as an emergent global health hazard, especially to pregnant women, the American College of Obstetricians and Gynecologists and the American Society for Reproductive Medicine have both joined the American Academy of Pediatrics and numerous other health professional organizations in calling for timely action to identify and reduce exposure to toxic environmental agents while addressing the consequences of such exposure [90]. In addition, the International Federation of Gynecology and Obstetrics (FIGO) also published an opinion on the reproductive health impacts of exposure to toxic environmental chemicals and stressed the role of reproductive health professionals in prioritizing preventing exposure to environmental chemicals everywhere [91]. These recommendations highlight the importance of training obstetricians on recognizing sources of exposure and identifying women at risk to feel better equipped to counsel these patients.

5. Conclusion

In this review, we summarize the most important endocrine disruptors and their effects on the fetus, mother, and pregnancy following in-utero exposure. The prenatal period represents a sensitive window that should not be overlooked, and the potential harmful effects of EDs should not be understated. Despite the seriousness of this matter, it remains challenging to draw strong conclusions about EDs effects from the available literature. We urge providers to be vigilant and dedicate more time to counseling pregnant women on EDs using what is currently available of evidence and guidelines, yet we stress the importance of conducting more research on EDs, with meticulous methodologies and careful sampling of subjects, in an attempt to produce a reliable body of evidence for future guidelines.

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References

1. International Programme on Chemical S. Global assessment on the state of the science of endocrine disruptors. Geneva: World Health Organization; 2002.
2. Kurowska P, Mlyczyńska E, Dawid M, Respekta N, Pich K, Serra L, et al. Endocrine disruptor chemicals, adipokines and reproductive functions. Endocrine. 2022;78(2):205-18. doi: 10.1007/s12020-022-03061-4.
3. Rolfo A, Nuzzo AM, De Amicis R, Moretti L, Bertoli S, Leone A. Fetal-Maternal Exposure to Endocrine Disruptors: Correlation with Diet Intake and Pregnancy Outcomes. Nutrients. 2020;12(6). doi: 10.3390/nu12061744.
4. Calkins K, Devaskar SU. Fetal origins of adult disease. Curr Probl Pediatr Adolesc Health Care. 2011;41(6):158-76. doi: 10.1016/j.cppeds.2011.01.001.
5. Duh-Leong C, Maffini MV, Kassotis CD, Vandenberg LN, Trasande L. The regulation of endocrine-disrupting chemicals to minimize their impact on health. Nature Reviews Endocrinology. 2023;19(10):600-14. doi: 10.1038/s41574-023-00872-x.
6. Street ME, Bernasconi S. Endocrine-Disrupting Chemicals in Human Fetal Growth. Int J Mol Sci. 2020;21(4). doi: 10.3390/ijms21041430.
7. Yan Y, Guo F, Liu K, Ding R, Wang Y. The effect of endocrine-disrupting chemicals on placental development. Front Endocrinol (Lausanne). 2023;14:1059854. doi: 10.3389/fendo.2023.1059854.
8. Xu X, Yekeen TA, Xiao Q, Wang Y, Lu F, Huo X. Placental IGF-1 and IGFBP-3 expression correlate with umbilical cord blood PAH and PBDE levels from prenatal exposure to electronic waste. Environmental Pollution. 2013;182:63-9. doi: https://doi.org/10.1016/j.envpol.2013.07.005.
9. Pacyga DC, Sathyanarayana S, Strakovsky RS. Dietary Predictors of Phthalate and Bisphenol Exposures in Pregnant Women. Adv Nutr. 2019;10(5):803-15. doi: 10.1093/advances/nmz029.
10. Geens T, Aerts D, Berthot C, Bourguignon J-P, Goeyens L, Lecomte P, et al. A review of dietary and non-dietary exposure to bisphenol-A. Food and Chemical Toxicology. 2012;50(10):3725-40. doi: https://doi.org/10.1016/j.fct.2012.07.059.
11. Bisphenol A: EU ban on baby bottles to enter into force tomorrow [Internet]. 2011. Available from: https://ec.europa.eu/commission/presscorner/detail/en/IP_11_664
12. Huang R-p, Liu Z-h, Yuan S-f, Yin H, Dang Z, Wu P-x. Worldwide human daily intakes of bisphenol A (BPA) estimated from global urinary concentration data (2000–2016) and its risk analysis. Environmental Pollution. 2017;230:143-52. doi: https://doi.org/10.1016/j.envpol.2017.06.026.
13. Harley KG, Aguilar Schall R, Chevrier J, Tyler K, Aguirre H, Bradman A, et al. Prenatal and postnatal bisphenol A exposure and body mass index in childhood in the CHAMACOS cohort. Environ Health Perspect. 2013;121(4):514-20. doi: 10.1289/ehp.1205548.
14. Liu J, Yu P, Qian W, Li Y, Zhao J, Huan F, et al. Perinatal bisphenol A exposure and adult glucose homeostasis: identifying critical windows of exposure. PLoS One. 2013;8(5):e64143. doi: 10.1371/journal.pone.0064143.
15. Valvi D, Casas M, Mendez MA, Ballesteros-Gómez A, Luque N, Rubio S, et al. Prenatal bisphenol a urine concentrations and early rapid growth and overweight risk in the offspring. Epidemiology. 2013;24(6):791-9. doi: 10.1097/EDE.0b013e3182a67822.
16. Braun JM, Lanphear BP, Calafat AM, Deria S, Khoury J, Howe CJ, Venners SA. Early-life bisphenol a exposure and child body mass index: a prospective cohort study. Environ Health Perspect. 2014;122(11):1239-45. doi: 10.1289/ehp.1408258.
17. Chevrier J, Gunier RB, Bradman A, Holland NT, Calafat AM, Eskenazi B, Harley KG. Maternal urinary bisphenol a during pregnancy and maternal and neonatal thyroid function in the CHAMACOS study. Environ Health Perspect. 2013;121(1):138-44. doi: 10.1289/ehp.1205092.
18. Berger K, Eskenazi B, Kogut K, Parra K, Lustig RH, Greenspan LC, et al. Association of Prenatal Urinary Concentrations of Phthalates and Bisphenol A and Pubertal Timing in Boys and Girls. Environ Health Perspect. 2018;126(9):97004. doi: 10.1289/ehp3424.
19. Barrett ES, Sathyanarayana S, Mbowe O, Thurston SW, Redmon JB, Nguyen RHN, Swan SH. First-Trimester Urinary Bisphenol A Concentration in Relation to Anogenital Distance, an Androgen-Sensitive Measure of Reproductive Development, in Infant Girls. Environ Health Perspect. 2017;125(7):077008. doi: 10.1289/ehp875.

20. Blaauwendraad SM, Gaillard R, Santos S, Sol CM, Kannan K, Trasande L, Jaddoe VWV. Maternal Phthalate and Bisphenol Urine Concentrations during Pregnancy and Early Markers of Arterial Health in Children. Environ Health Perspect. 2022;130(4):47007. doi: 10.1289/ehp10293.
21. Grohs MN, Reynolds JE, Liu J, Martin JW, Pollock T, Lebel C, Dewey D. Prenatal maternal and childhood bisphenol a exposure and brain structure and behavior of young children. Environ Health. 2019;18(1):85. doi: 10.1186/s12940-019-0528-9.
22. Braun JM, Muckle G, Arbuckle T, Bouchard MF, Fraser WD, Ouellet E, et al. Associations of Prenatal Urinary Bisphenol A Concentrations with Child Behaviors and Cognitive Abilities. Environ Health Perspect. 2017;125(6):067008. doi: 10.1289/ehp984.
23. Hansen JB, Bilenberg N, Timmermann CAG, Jensen RC, Frederiksen H, Andersson AM, et al. Prenatal exposure to bisphenol A and autistic- and ADHD-related symptoms in children aged 2 and5 years from the Odense Child Cohort. Environ Health. 2021;20(1):24. doi: 10.1186/s12940-021-00709-y.
24. Jukic AM, Calafat AM, McConnaughey DR, Longnecker MP, Hoppin JA, Weinberg CR, et al. Urinary Concentrations of Phthalate Metabolites and Bisphenol A and Associations with Follicular-Phase Length, Luteal-Phase Length, Fecundability, and Early Pregnancy Loss. Environ Health Perspect. 2016;124(3):321-8. doi: 10.1289/ehp.1408164.
25. Leclerc F, Dubois M-F, Aris A. Maternal, placental and fetal exposure to bisphenol A in women with and without preeclampsia. Hypertension in Pregnancy. 2014;33(3):341-8. doi: 10.3109/10641955.2014.892607.
26. Cantonwine DE, Meeker JD, Ferguson KK, Mukherjee B, Hauser R, McElrath TF. Urinary Concentrations of Bisphenol A and Phthalate Metabolites Measured during Pregnancy and Risk of Preeclampsia. Environ Health Perspect. 2016;124(10):1651-5. doi: 10.1289/ehp188.
27. Cantonwine DE, Ferguson KK, Mukherjee B, McElrath TF, Meeker JD. Urinary Bisphenol A Levels during Pregnancy and Risk of Preterm Birth. Environ Health Perspect. 2015;123(9):895-901. doi: 10.1289/ehp.1408126.
28. Cantonwine D, Meeker JD, Hu H, Sánchez BN, Lamadrid-Figueroa H, Mercado-García A, et al. Bisphenol a exposure in Mexico City and risk of prematurity: a pilot nested case control study. Environ Health. 2010;9:62. doi: 10.1186/1476-069x-9-62.
29. Snijder CA, Heederik D, Pierik FH, Hofman A, Jaddoe VW, Koch HM, et al. Fetal growth and prenatal exposure to bisphenol A: the generation R study. Environ Health Perspect. 2013;121(3):393-8. doi: 10.1289/ehp.1205296.
30. Huo W, Xia W, Wan Y, Zhang B, Zhou A, Zhang Y, et al. Maternal urinary bisphenol A levels and infant low birth weight: A nested case-control study of the Health Baby Cohort in China. Environ Int. 2015;85:96-103. doi: 10.1016/j.envint.2015.09.005.
31. Lee BE, Park H, Hong YC, Ha M, Kim Y, Chang N, et al. Prenatal bisphenol A and birth outcomes: MOCEH (Mothers and Children's Environmental Health) study. Int J Hyg Environ Health. 2014;217(2-3):328-34. doi: 10.1016/j.ijheh.2013.07.005.
32. Philippat C, Mortamais M, Chevrier C, Petit C, Calafat AM, Ye X, et al. Exposure to phthalates and phenols during pregnancy and offspring size at birth. Environ Health Perspect. 2012;120(3):464-70. doi: 10.1289/ehp.1103634.
33. Hu J, Zhao H, Braun Joseph M, Zheng T, Zhang B, Xia W, et al. Associations of Trimester-Specific Exposure to Bisphenols with Size at Birth: A Chinese Prenatal Cohort Study. Environmental Health Perspectives.127(10):107001. doi: 10.1289/EHP4664.
34. Casas M, Valvi D, Ballesteros-Gomez A, Gascon M, Fernández MF, Garcia-Esteban R, et al. Exposure to Bisphenol A and Phthalates during Pregnancy and Ultrasound Measures of Fetal Growth in the INMA-Sabadell Cohort. Environ Health Perspect. 2016;124(4):521-8. doi: 10.1289/ehp.1409190.
35. Cathey AL, Watkins DJ, Rosario ZY, Vélez C, Mukherjee B, Alshawabkeh AN, et al. Biomarkers of Exposure to Phthalate Mixtures and Adverse Birth Outcomes in a Puerto Rico Birth Cohort. Environ Health Perspect. 2022;130(3):37009. doi: 10.1289/ehp8990.
36. Huang HB, Chen HY, Su PH, Huang PC, Sun CW, Wang CJ, et al. Fetal and Childhood Exposure to Phthalate Diesters and Cognitive Function in Children Up to 12 Years of Age: Taiwanese Maternal and Infant Cohort Study. PLoS One. 2015;10(6):e0131910. doi: 10.1371/journal.pone.0131910.
37. Wang X, Wang LL, Tian YK, Xiong SM, Liu YJ, Zhang HN, et al. Association between exposures to phthalate metabolites and preterm birth and spontaneous preterm birth: A systematic review and meta-analysis. Reprod Toxicol. 2022;113:1-9. doi: 10.1016/j.reprotox.2022.07.006.

38. Ferguson KK, Rosen EM, Rosario Z, Feric Z, Calafat AM, McElrath TF, et al. Environmental phthalate exposure and preterm birth in the PROTECT birth cohort. Environ Int. 2019;132:105099. doi: 10.1016/j.envint.2019.105099.
39. Ferguson KK, McElrath TF, Meeker JD. Environmental phthalate exposure and preterm birth. JAMA Pediatr. 2014;168(1):61-7. doi: 10.1001/jamapediatrics.2013.3699.
40. Hu JMY, Arbuckle TE, Janssen P, Lanphear BP, Braun JM, Platt RW, et al. Associations of prenatal urinary phthalate exposure with preterm birth: the Maternal-Infant Research on Environmental Chemicals (MIREC) Study. Can J Public Health. 2020;111(3):333-41. doi: 10.17269/s41997-020-00322-5.
41. Ferguson KK, McElrath TF, Chen YH, Mukherjee B, Meeker JD. Urinary phthalate metabolites and biomarkers of oxidative stress in pregnant women: a repeated measures analysis. Environ Health Perspect. 2015;123(3):210-6. doi: 10.1289/ehp.1307996.
42. Holland N, Huen K, Tran V, Street K, Nguyen B, Bradman A, Eskenazi B. Urinary Phthalate Metabolites and Biomarkers of Oxidative Stress in a Mexican-American Cohort: Variability in Early and Late Pregnancy. Toxics. 2016;4(1). doi: 10.3390/toxics4010007.
43. Zhang M, Qiao J, Xie P, Li Z, Hu C, Li F. The Association between Maternal Urinary Phthalate Concentrations and Blood Pressure in Pregnancy: A Systematic Review and Meta-Analysis. Metabolites. 2023;13(7). doi: 10.3390/metabo13070812.
44. Werner EF, Braun JM, Yolton K, Khoury JC, Lanphear BP. The association between maternal urinary phthalate concentrations and blood pressure in pregnancy: The HOME Study. Environ Health. 2015;14:75. doi: 10.1186/s12940-015-0062-3.
45. Wu H, Kupsco A, Just A, Calafat AM, Oken E, Braun JM, et al. Maternal Phthalates Exposure and Blood Pressure during and after Pregnancy in the PROGRESS Study. Environ Health Perspect. 2021;129(12):127007. doi: 10.1289/ehp8562.
46. Eberle C, Stichling S. Environmental health influences in pregnancy and risk of gestational diabetes mellitus: a systematic review. BMC Public Health. 2022;22(1):1572. doi: 10.1186/s12889-022-13965-5.
47. Huang PC, Tsai CH, Liang WY, Li SS, Huang HB, Kuo PL. Early Phthalates Exposure in Pregnant Women Is Associated with Alteration of Thyroid Hormones. PLoS One. 2016;11(7):e0159398. doi: 10.1371/journal.pone.0159398.
48. Johns LE, Ferguson KK, McElrath TF, Mukherjee B, Meeker JD. Associations between Repeated Measures of Maternal Urinary Phthalate Metabolites and Thyroid Hormone Parameters during Pregnancy. Environ Health Perspect. 2016;124(11):1808-15. doi: 10.1289/ehp170.
49. Kuo FC, Su SW, Wu CF, Huang MC, Shiea J, Chen BH, et al. Relationship of urinary phthalate metabolites with serum thyroid hormones in pregnant women and their newborns: a prospective birth cohort in Taiwan. PLoS One. 2015;10(6):e0123884. doi: 10.1371/journal.pone.0123884.
50. Li J, Qian X, Zhou Y, Li Y, Xu S, Xia W, Cai Z. Trimester-specific and sex-specific effects of prenatal exposure to di(2-ethylhexyl) phthalate on fetal growth, birth size, and early-childhood growth: A longitudinal prospective cohort study. Sci Total Environ. 2021 Jul 10;777:146146. doi: 10.1016/j.scitotenv.2021.146146.
51. Shen R, Zhao LL, Yu Z, Zhang C, Chen YH, Wang H, et al. Maternal di-(2-ethylhexyl) phthalate exposure during pregnancy causes fetal growth restriction in a stage-specific but gender-independent manner. Reprod Toxicol. 2017;67:117-24. doi: 10.1016/j.reprotox.2016.12.003.
52. Ferguson KK, Meeker JD, Cantonwine DE, Chen YH, Mukherjee B, McElrath TF. Urinary phthalate metabolite and bisphenol A associations with ultrasound and delivery indices of fetal growth. Environ Int. 2016;94:531-7. doi: 10.1016/j.envint.2016.06.013.
53. Puche-Juarez M, Toledano JM, Moreno-Fernandez J, Gálvez-Ontiveros Y, Rivas A, Diaz-Castro J, Ochoa JJ. The Role of Endocrine Disrupting Chemicals in Gestation and Pregnancy Outcomes. Nutrients. 2023;15(21). doi: 10.3390/nu15214657.
54. Cho S-C, Bhang S-Y, Hong Y-C, Shin M-S, Kim B-N, Kim J-W, et al. Relationship between Environmental Phthalate Exposure and the Intelligence of School-Age Children. Environmental Health Perspectives. 2010;118(7):1027-32. doi: 10.1289/ehp.0901376.
55. Polanska K, Ligocka D, Sobala W, Hanke W. Phthalate exposure and child development: The Polish Mother and Child Cohort Study. Early Human Development. 2014;90(9):477-85. doi: https://doi.org/10.1016/j.earlhumdev.2014.06.006.

56. Téllez-Rojo MM, Cantoral A, Cantonwine DE, Schnaas L, Peterson K, Hu H, Meeker JD. Prenatal urinary phthalate metabolites levels and neurodevelopment in children at two and three years of age. Science of The Total Environment. 2013;461-462:386-90. doi: https://doi.org/10.1016/j.scitotenv.2013.05.021.
57. Whyatt Robin M, Liu X, Rauh Virginia A, Calafat Antonia M, Just Allan C, Hoepner L, et al. Maternal Prenatal Urinary Phthalate Metabolite Concentrations and Child Mental, Psychomotor, and Behavioral Development at 3 Years of Age. Environmental Health Perspectives. 2012;120(2):290-5. doi: 10.1289/ehp.1103705.
58. Shin HM, Schmidt RJ, Tancredi D, Barkoski J, Ozonoff S, Bennett DH, Hertz-Picciotto I. Prenatal exposure to phthalates and autism spectrum disorder in the MARBLES study. Environ Health. 2018;17(1):85. doi: 10.1186/s12940-018-0428-4.
59. Oulhote Y, Lanphear B, Braun JM, Webster GM, Arbuckle TE, Etzel T, et al. Gestational Exposures to Phthalates and Folic Acid, and Autistic Traits in Canadian Children. Environ Health Perspect. 2020;128(2):27004. doi: 10.1289/ehp5621.
60. Kaushal J, Khatri M, Arya SK. A treatise on Organophosphate pesticide pollution: Current strategies and advancements in their environmental degradation and elimination. Ecotoxicology and Environmental Safety. 2021;207:111483. doi: https://doi.org/10.1016/j.ecoenv.2020.111483.
61. Delfino RT, Ribeiro TS, Figueroa-Villar JD. Organophosphorus compounds as chemical warfare agents: a review. Journal of the Brazilian Chemical Society. 2009;20.
62. Bi R, Meng W, Su G. Organophosphate esters (OPEs) in plastic food packaging: non-target recognition, and migration behavior assessment. Environment International. 2023;177:108010. doi: https://doi.org/10.1016/j.envint.2023.108010.
63. Gunier RB, Bradman A, Harley KG, Kogut K, Eskenazi B. Prenatal Residential Proximity to Agricultural Pesticide Use and IQ in 7-Year-Old Children. Environ Health Perspect. 2017;125(5):057002. doi: 10.1289/ehp504.
64. Wang A, Wan Y, Mahai G, Qian X, Li Y, Xu S, Xia W. Association of Prenatal Exposure to Organophosphate, Pyrethroid, and Neonicotinoid Insecticides with Child Neurodevelopment at 2 Years of Age: A Prospective Cohort Study. Environ Health Perspect. 2023;131(10):107011. doi: 10.1289/ehp12097.
65. Bliznashka L, Roy A, Christiani DC, Calafat AM, Ospina M, Diao N, et al. Pregnancy pesticide exposure and child development in low- and middle-income countries: A prospective analysis of a birth cohort in rural Bangladesh and meta-analysis. PLoS One. 2023;18(6):e0287089. doi: 10.1371/journal.pone.0287089.
66. Cartier C, Warembourg C, Le Maner-Idrissi G, Lacroix A, Rouget F, Monfort C, et al. Organophosphate Insecticide Metabolites in Prenatal and Childhood Urine Samples and Intelligence Scores at 6 Years of Age: Results from the Mother-Child PELAGIE Cohort (France). Environ Health Perspect. 2016;124(5):674-80. doi: 10.1289/ehp.1409472.
67. Jusko TA, van den Dries MA, Pronk A, Shaw PA, Guxens M, Spaan S, et al. Organophosphate Pesticide Metabolite Concentrations in Urine during Pregnancy and Offspring Nonverbal IQ at Age 6 Years. Environ Health Perspect. 2019;127(1):17007. doi: 10.1289/ehp3024.
68. Engel SM, Berkowitz GS, Barr DB, Teitelbaum SL, Siskind J, Meisel SJ, et al. Prenatal organophosphate metabolite and organochlorine levels and performance on the Brazelton Neonatal Behavioral Assessment Scale in a multiethnic pregnancy cohort. Am J Epidemiol. 2007;165(12):1397-404. doi: 10.1093/aje/kwm029.
69. Bouchard MF, Chevrier J, Harley KG, Kogut K, Vedar M, Calderon N, et al. Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children. Environ Health Perspect. 2011;119(8):1189-95. doi: 10.1289/ehp.1003185.
70. Zhang Y, Han S, Liang D, Shi X, Wang F, Liu W, et al. Prenatal exposure to organophosphate pesticides and neurobehavioral development of neonates: a birth cohort study in Shenyang, China. PLoS One. 2014;9(2):e88491. doi: 10.1371/journal.pone.0088491.
71. Shelton JF, Geraghty EM, Tancredi DJ, Delwiche LD, Schmidt RJ, Ritz B, et al. Neurodevelopmental disorders and prenatal residential proximity to agricultural pesticides: the CHARGE study. Environ Health Perspect. 2014;122(10):1103-9. doi: 10.1289/ehp.1307044.
72. Sagiv SK, Harris MH, Gunier RB, Kogut KR, Harley KG, Deardorff J, et al. Prenatal Organophosphate Pesticide Exposure and Traits Related to Autism Spectrum Disorders in a Population Living in Proximity to Agriculture. Environ Health Perspect. 2018;126(4):047012. doi: 10.1289/ehp2580.

73. Schmidt RJ, Kogan V, Shelton JF, Delwiche L, Hansen RL, Ozonoff S, et al. Combined Prenatal Pesticide Exposure and Folic Acid Intake in Relation to Autism Spectrum Disorder. Environ Health Perspect. 2017;125(9):097007. doi: 10.1289/ehp604.
74. Harley KG, Engel SM, Vedar MG, Eskenazi B, Whyatt RM, Lanphear BP, et al. Prenatal Exposure to Organophosphorous Pesticides and Fetal Growth: Pooled Results from Four Longitudinal Birth Cohort Studies. Environ Health Perspect. 2016;124(7):1084-92. doi: 10.1289/ehp.1409362.
75. Dalsager L, Christensen LE, Kongsholm MG, Kyhl HB, Nielsen F, Schoeters G, et al. Associations of maternal exposure to organophosphate and pyrethroid insecticides and the herbicide 2,4-D with birth outcomes and anogenital distance at 3 months in the Odense Child Cohort. Reprod Toxicol. 2018;76:53-62. doi: 10.1016/j.reprotox.2017.12.008.
76. Ferguson KK, van den Dries MA, Gaillard R, Pronk A, Spaan S, Tiemeier H, Jaddoe VWV. Organophosphate Pesticide Exposure in Pregnancy in Association with Ultrasound and Delivery Measures of Fetal Growth. Environ Health Perspect. 2019;127(8):87005. doi: 10.1289/ehp4858.
77. Rahman MF, Peldszus S, Anderson WB. Behaviour and fate of perfluoroalkyl and polyfluoroalkyl substances (PFASs) in drinking water treatment: A review. Water Research. 2014;50:318-40. doi: https://doi.org/10.1016/j.watres.2013.10.045.
78. Szilagyi JT, Avula V, Fry RC. Perfluoroalkyl Substances (PFAS) and Their Effects on the Placenta, Pregnancy, and Child Development: a Potential Mechanistic Role for Placental Peroxisome Proliferator-Activated Receptors (PPARs). Curr Environ Health Rep. 2020;7(3):222-30. doi: 10.1007/s40572-020-00279-0.
79. Jensen TK, Andersen LB, Kyhl HB, Nielsen F, Christesen HT, Grandjean P. Association between perfluorinated compound exposure and miscarriage in Danish pregnant women. PLoS One. 2015;10(4):e0123496. doi: 10.1371/journal.pone.0123496.
80. Shin HM, Oh J, R JS, E NP. Prenatal Exposure to Per- and Polyfluoroalkyl Substances, Maternal Thyroid Dysfunction, and Child Autism Spectrum Disorder. Endocrinol Metab (Seoul). 2022;37(6):819-29. doi: 10.3803/EnM.2022.1598.
81. Frangione B, Birk S, Benzouak T, Rodriguez-Villamizar LA, Karim F, Dugandzic R, Villeneuve PJ. Exposure to perfluoroalkyl and polyfluoroalkyl substances and pediatric obesity: a systematic review and meta-analysis. Int J Obes (Lond). 2024;48(2):131-46. doi: 10.1038/s41366-023-01401-6.
82. Stratakis N, Rock S, La Merrill MA, Saez M, Robinson O, Fecht D, et al. Prenatal exposure to persistent organic pollutants and childhood obesity: A systematic review and meta-analysis of human studies. Obes Rev. 2022;23 Suppl 1(Suppl 1):e13383. doi: 10.1111/obr.13383.
83. Frigerio G, Ferrari CM, Fustinoni S. Prenatal and childhood exposure to per-/polyfluoroalkyl substances (PFASs) and its associations with childhood overweight and/or obesity: a systematic review with meta-analyses. Environ Health. 2023;22(1):56. doi: 10.1186/s12940-023-01006-6.
84. Gui SY, Chen YN, Wu KJ, Liu W, Wang WJ, Liang HR, et al. Association Between Exposure to Per- and Polyfluoroalkyl Substances and Birth Outcomes: A Systematic Review and Meta-Analysis. Front Public Health. 2022;10:855348. doi: 10.3389/fpubh.2022.855348.
85. Zhang Y, Mustieles V, Sun Q, Coull B, McElrath T, Rifas-Shiman SL, et al. Association of Early Pregnancy Perfluoroalkyl and Polyfluoroalkyl Substance Exposure With Birth Outcomes. JAMA Netw Open. 2023;6(5):e2314934. doi: 10.1001/jamanetworkopen.2023.14934.
86. Forns J, Verner MA, Iszatt N, Nowack N, Bach CC, Vrijheid M, et al. Early Life Exposure to Perfluoroalkyl Substances (PFAS) and ADHD: A Meta-Analysis of Nine European Population-Based Studies. Environ Health Perspect. 2020;128(5):57002. doi: 10.1289/ehp5444.
87. Yao H, Fu Y, Weng X, Zeng Z, Tan Y, Wu X, et al. The Association between Prenatal Per- and Polyfluoroalkyl Substances Exposure and Neurobehavioral Problems in Offspring: A Meta-Analysis. Int J Environ Res Public Health. 2023;20(3). doi: 10.3390/ijerph20031668.
88. Tillaut H, Monfort C, Rouget F, Pelé F, Lainé F, Gaudreau E, et al. Prenatal Exposure to Perfluoroalkyl Substances and Child Behavior at Age 12: A PELAGIE Mother–Child Cohort Study. Environmental Health Perspectives. 2023;131(11):117009. doi: doi:10.1289/EHP12540.
89. Bellingham MS, R. M. Chemical Exposures During Pregnancy: Dealing with Potential, but Unproven, Risks to Child Health. Scientific Impact Paper 37. 2013.

 doi:10.20944/preprints202408.0923.v1

90. Reducing Prenatal Exposure to Toxic Environmental Agents: ACOG Committee Opinion, Number 832. Obstet Gynecol. 2021;138(1):e40-e54. doi: 10.1097/aog.0000000000004449.
91. Di Renzo GC, Conry JA, Blake J, DeFrancesco MS, DeNicola N, Martin JN, Jr., et al. International Federation of Gynecology and Obstetrics opinion on reproductive health impacts of exposure to toxic environmental chemicals. Int J Gynaecol Obstet. 2015;131(3):219-25. doi: 10.1016/j.ijgo.2015.09.002.