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Environmental Toxicant Exposure and Hypertensive Disorders of Pregnancy: Recent Findings

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Abstract

Purpose of Review—To assess the strength of evidence for associations between environmental toxicants and hypertensive disorders of pregnancy, suggest potential biological mechanisms based on animal and in vitro studies, and highlight avenues for future research.

Recent Findings—Evidence is strongest for links between persistent chemicals, including lead, cadmium, organochlorine pesticides, and polycyclic biphenyls, and preeclampsia, although associations are sometimes not detectable at low-exposure levels. Results have been inconclusive for bisphenols, phthalates, and organophosphates. Biological pathways may include oxidative stress, epigenetic changes, endocrine disruption, and abnormal placental vascularization. Additional prospective epidemiologic studies beginning in the preconception period and extending postpartum are needed to assess the life course trajectory of environmental exposures and women's reproductive and cardiovascular health. Future studies should also consider interactions between chemicals and consider nonlinear associations.

Summary—These results confirm recommendations by the International Federation of Gynecology and Obstetrics, the American Society for Reproductive Medicine, the American Academy of Pediatrics, and the Endocrine Society that providers counsel their pregnant patients to limit exposure to environmental toxicants.

Keywords

Endocrine disruptors; Environmental exposures; Heavy metals; Pesticides; Bisphenol A; Preeclampsia; Gestational hypertension

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Conflict of Interest The authors declare that they have no conflicts of interest.

Compliance with Ethical Standards

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Environmental toxicants have been linked to a wide range of adverse chronic health outcomes across various biological systems [1], with negative health and economic consequences for individuals and society [2, 3]. Prenatal exposure to these chemicals is of particular concern, as gestation represents a critical period in which fetal organs may be programmed in ways that permanently affect health and development. Indeed, a recent review found that prenatal exposure to more than 60 different chemicals have been evaluated with reference to child health outcomes in more than a dozen categories, including neurological/cognitive, cancer, respiratory, growth/metabolism, reproduction, immune, endocrine, and cardiovascular [4]. Pregnancy is a critical period not only for fetal and child health, however; mounting evidence suggests that maternal postnatal health may also be affected by changes that occur during the prenatal period. In particular, women diagnosed with hypertensive disorders of pregnancy (HDP), including gestational hypertension, preeclampsia, and eclampsia, have increased risk of cardiovascular disease (CVD) later in life [5, 6]. Whether or not environmental toxicants may increase the risk of HDP—and consequently the risk of maternal postpartum CVD—is an emerging question in the epidemiologic literature. The current review summarizes recent reports of associations of environmental chemicals with HDP, discusses biological mechanisms that may underlie these associations, and suggests avenues for future research.

Hypertensive Disorders of Pregnancy: An Increasingly Urgent Problem

Hypertensive disorders of pregnancy (HDP) are a significant public health concern, as they are not only leading contributors to maternal, fetal, and neonatal morbidity and mortality, but also have potentially long-term effects on the health of women, more than doubling their risk of diagnosed CVD, the leading cause of death for women in the USA [7]. In a meta-analysis of data from 43 studies, Brown et al. reported that, compared to women without HDP, women with a history of preeclampsia or eclampsia had 2.28 times the odds of fatal or diagnosed CVD (95% confidence interval, in brackets henceforth, [1.87, 2.78]), 1.76 times the odds of cerebrovascular disease [1.43, 2.21], and 3.13 times the risk of hypertension [2.51, 3.89] diagnosed at least 6 weeks postpartum [5]. In a meta-analysis of 22 studies focused exclusively on preeclampsia, Wu et al. reported that women with a history of preeclampsia had increased risk of future heart failure (risk ratio [RR] = 4.19 [2.09, 8.38]), coronary heart disease (RR = 2.50 [1.43, 4.37]), death from CVD (RR = 2.21 [1.83, 2.66]), and stroke (RR = 1.81 [1.29, 2.55]) [6]. Among 58,671 primiparous Nurses' Health Study II participants, gestational hypertension and preeclampsia were also associated with increased likelihood of CVD risk factors such as chronic hypertension (hazard ratio [HR] = 2.8 [2.6, 3.0] and 2.2 [2.1, 2.3], respectively), type 2 diabetes (HR = 1.7 [1.4, 1.9] and 1.8 [1.6, 1.9], respectively), and hypercholesterolemia (HR = 1.4 [1.3, 1.5] and 1.3 [1.3, 1.4], respectively) [8].

Rates of HDP in the USA increased 73% between 1993 and 2014, reaching 912/10,000 delivery hospitalizations according to the most recent data available [9]. Between 2011 and 2013, HDP caused 7.4% of pregnancy-related deaths, which are also on the rise according to data from the US Centers for Disease Control and Prevention [10]. HDP incidence in

the USA has increased in tandem with a number of known risk factors for the conditions, including advanced maternal age, nulliparity, multifetal gestation, increased body mass index, pregestational diabetes, and chronic hypertension [11, 12]. Only recently has attention turned to the potential contribution of environmental toxicants, including heavy metals, persistent organic pollutants (POPs), and nonpersistent chemicals, to HDP.

Environmental Chemicals and CVD

Studies have identified environmental toxicants as risk factors for CVD in non-pregnant adults. Toxic heavy metals such as arsenic, cadmium, chromium, lead, and mercury, have been linked to atherosclerosis [13], hypertension [14–16], and clinical CVD [17–19]. Research into accidental, occupational, and industrial waste exposure to POPs, such as dioxins and polychlorinated biphenyls, has demonstrated associations with increased incidence of CVD [20–23]. The last decade has seen an explosion of interest in nonpersistent environmental chemicals, urinary metabolites of which are detectable in the vast majority of the US population [24–26]. Human and animal studies have reported associations of nonpersistent chemicals such as bisphenol A (BPA) and organophosphate (OP) metabolites with CVD and its preconditions, such as obesity and type 2 diabetes [27–29], although results for phthalates have been less consistent [30]. Because CVD and HDP have numerous risk factors in common, including elevated blood pressure, obesity, dyslipidemia, insulin resistance, hyperglycemia, inflammation, endothelial dysfunction, hyperuricemia, hyperhomocysteinemia, thrombosis, and angiogenesis [31], it is possible that the biological mechanisms by which environmental chemicals increase the risk of CVD may also increase the risk of HDP. In particular, the endocrine-disrupting properties of many of these chemicals may make exposure to them particularly disruptive during the hormonally sensitive prenatal period.

The Placental Connection

HDP are the extreme manifestation of a continuum of abnormal placental development and function. The placenta is a hybrid organ, comprising tissue from both woman and fetus. As such, it the nexus of interaction between them, providing oxygen, nutrients, immunological and hormonal support to the fetus, and removing waste from its blood. This exchange occurs via a network of specialized vasculature. Healthy development of the placenta is essential to optimal fetal growth, and inadequate vascular proliferation can lead to underperfusion of the placenta, potentially resulting in intrauterine growth restriction and adverse pregnancy outcomes, specifically HDP [32]. Placental dysfunction may also occur when the placenta has not implanted correctly in the uterine lining. Fetal trophoblasts must invade the maternal myometrium to a particular depth in order to stimulate the remodeling of maternal spiral arteries into low-resistance vessels that optimize maternal-fetal blood flow [33]. Inadequate invasion may lead to increased resistance in the uterine arteries and elevated maternal blood pressure. In evaluating the potential contribution of environmental toxicants to placental dysfunction, it is therefore important to assess associations not only with diagnosed HDP, but with subclinical outcomes that may lie along the causal pathway to HDP, including maternal serum levels of pro- and antiangiogenic factors, maternal blood pressure, and placental hemodynamic measures.

Recent Studies of Environmental Toxicants, HDP, and Related Outcomes

Over the past 3 years, a number of published studies have examined associations of environmental toxicants with HDP. While the emphasis has been greater on heavy metals and POPs, attention to nonpersistent chemicals is beginning to grow. At the same time, there has been a notable uptick in studies considering outcomes suggestive of potential biological mechanisms, especially epigenetic markers. Below we review these recent additions to the literature.

Heavy Metals

Although exposure to heavy metals has declined in economically developed countries, it is still a cause for concern in many parts of the world. Arsenic, lead, and mercury are the top three substances on the 2017 Agency for Toxic Substances and Disease Registry (ATSDR) Priority List of Hazardous Substances [34]. All three, along with cadmium (number 7 on the list), have been shown to increase mortality from CVD in large epidemiologic studies [13]. It is therefore plausible that exposure during pregnancy might influence placental development and function in a way that may predispose women to HDP.

For more than a century, *lead* has been linked to increased risk of preeclampsia. A systematic review and meta-analysis recently reported that an increase of 1 μg/dL blood lead was associated with a 1.6% increase in likelihood of preeclampsia, making lead exposure one of the strongest known risk factors for preeclampsia [35]. Two recent papers not included in this review confirm its findings. In a case-control study of 158 women conducted from 2015 to 2016 in Zanjan, Iran, Bayat et al., found preeclamptic women to have significantly higher adjusted third trimester mean blood lead level than women with normal deliveries [36]. Although the authors did adjust for maternal age, education, and income, they did not match on or control for gestational age, nor did they test for interaction by infant sex, which was associated with the outcome. In Kinshasa, the capital of the Democratic Republic of Congo, incidence of preeclampsia is high, as is exposure to heavy metals from traffic pollution, waste disposal, battery recycling, and other unregulated activities. In a case-control study conducted there by Elongi Moyene et al., excretion of lead in 24-h urine samples among 82 preeclamptic and 6 eclamptic women was 6.7 times higher than in 88 community controls matched on a number of variables [37•]. Although blood lead is the preferred measure of recent exposure, 24-h urinary excretion measures are a valid alternative and obviate the need for creatinine adjustment, which is controversial during pregnancy because of changes in the glomerular filtration rate. By contrast, Maduray et al. did not find an association between lead measured either in blood or in pubic hair at delivery in a case-control study of 43 preeclamptic and 23 normotensive women in the more economically advantaged region of KwaZulu-Natal, South Africa, but did not adjust for any covariates in their analysis [38]. Hypothesized mechanisms by which elevated lead may induce preeclampsia include its positive association with the vasoconstrictors endothelin [39], adrenaline, and noradrenaline [40], and its negative association with nitric oxide [40] and adenosine triphosphatase [41], which are vasodilators.

Cadmium has also been recognized as a risk factor for preeclampsia for a number of decades. As with lead, Elongi Moyene et al. observed significantly higher urinary cadmium

levels among preeclamptic women [37•], but Maduray et al. did not [38]. In a case-control study nested within the Maternal Oral Therapy to Reduce Obstetric Risk study, cadmium measured in digested placental samples from 172 women from the Southeastern USA was associated with increased odds of preeclampsia (adjusted odds ratio [OR] = 1.5 [1.1, 2.2]) [42]. While the study was cross-sectional, cadmium's long half-life suggests that levels in placental tissue would suitably represent cumulative exposure throughout pregnancy. Among 132-matched cases and controls recruited from 2014 to 2016 in Zhejiang Province, China, Wang et al. found higher cadmium levels in both maternal blood and placental tissue of preeclamptic women compared to healthy pregnant women, but only third trimester blood concentration was significantly associated with preeclampsia after covariate adjustment (OR = 7.83 [1.64, 37.3]) [43]. The difference in size of the effect measure between the two studies results from the different biosamples in which cadmium was measured as well as different background rates of cadmium exposure. Cadmium's deleterious effect on placental function may stem from its role as a source of reactive oxygen species and oxidative stress [44]. It is also a source of pro-inflammatory cytokines, which may damage placental blood vessels and increase maternal blood pressure [45]. Animal studies suggest cadmium may induce preeclampsia by dysregulating immune function [46], increasing oxidative DNA damage in the placenta [47], and damaging the kidneys [48]. In vitro studies indicate that cadmium epigenetically upregulates expression of genes within the transforming growth factor-beta (TGFβ) pathway [49], inhibiting placental trophoblast cell migration [50].

Results of studies examining associations between *arsenic* and preeclampsia have been mixed. Elongi Moyene et al. noted a trend toward higher urinary excretion of arsenic among preeclamptic and eclamptic women [37•], but Maduray et al. did not [38]. In a case-control study of 104 preeclamptic women and 202 healthy women from the same hospital in Durango, Mexico, Sandoval-Carrillo et al. measured arsenic in spot urines prior to delivery as well as in water samples from drinking wells near participants' homes 1–3 weeks postpartum. They found no difference in odds of preeclampsia among tertiles of arsenic concentration in either medium [51]. The wells that provide drinking water to Durango have relatively low arsenic levels; future studies that are conducted in areas with higher arsenic contamination may have different results.

Both Elongi Moyene et al. and Maduray et al. observed higher levels of *chromium* among preeclamptic vs. normotensive women [37•, 38]. In the latter case, the difference was only observed for chromium measured in pubic hair, not in maternal blood. Both of these studies measured multiple heavy metals; neither conducted covariate-adjusted regression analyses much less any type of mixtures analysis to try to disentangle the effects of these highly correlated exposures.

Finally, a single recent analysis examined the role of *mercury* in preeclampsia. In a prospective cohort study conducted in Menoufia, Egypt, El-Badry et al. measured creatinine-adjusted urinary mercury concentration in all three trimesters among 124 pregnant dental staff and hospital administrators. The dental staff had significantly higher mercury concentrations throughout pregnancy, and 3.67 [1.25, 10.8] times the odds of preeclampsia compared to the administrators. They also had lower concentrations of two major antioxidant enzymes, glutathione peroxidase and superoxide dismutase, suggesting

that one of the ways mercury exposure may increase the risk of preeclampsia is by inducing oxidative stress [52•].

Persistent Organic Pollutants

POPs encompass several categories of compounds, including organochlorine (OC) pesticides such as dichlorodiphenyltrichloroethane (DDT), many of which are regulated or banned in various parts of the world; polybrominated diphenyl ethers (PBDEs), which are used as flame retardants in textiles, furnishings, electronics, and building materials; polychlorinated biphenyls (PCBs), which were primarily used as coolants and insulators in transformers and capacitors, as industrial lubricants, and as plasticizers in paint and flexible PVC until their production was banned in the 1970s; and perfluoroalkyl substances (PFAS), which endow carpets and fabrics with stainand water-resistance, are used to create nonstick surfaces, and are contained in fire-fighting foam. Because these chemicals persist in the natural environment—and, in the case of PCBs and PBDEs, are incorporated into the built environment—exposure continues long after production has been curtailed. Highly lipophilic, they bioaccumulate in fat tissue and move up the food chain. Notorious for their neuro-, immuno-, repro-, and genotoxic properties, as well as their links to various cancers, these chemicals are increasingly being examined for cardiovascular effects, as well [53], including HDP.

Under the Stockholm Convention on Persistent Organic Pollutants, originally ratified in 2004 and amended every 2 years beginning in 2009, 22 chemicals have thus far been targeted for elimination, including a majority of *OC pesticides.* Restricted application of DDT, which is used to control malaria in parts of the developing world, is still permitted. Kyrgyzstan, a former Soviet republic that is party to the convention, was the site of a recent cross-sectional study by Toichuev et al. that measured OC pesticides in 508 placentas from hospitals located in areas with high, medium, and low historic exposure. They examined 11 OC pesticides—the polyhalogenated compound hexachlorocyclohexane (HCH) and its isomers α-HCH, β-HCH, γ-HCH, and δ-HCH; p,p'-DDT and its contaminants dichlorodiphenyldichloroethylene (p,p'-DDE) and dichlorodiphenyldichloroethane (p,p'-DDD); aldrin; dieldrin; and heptachlor—and categorized women as unexposed (levels below the limit of detection) or exposed. Exposed women had ten times the risk of preeclampsia or eclampsia compared to unexposed women (7.5% vs. 0.75%); the researchers did not have access to women's personal data and could therefore not control for confounders [54]. In a cross-sectional study of 733 women recruited from a rural hospital in Limpopo Province, South Africa, Murray et al. found that higher serum p,p'-DDT and p,p'-DDE exposure was associated with higher adjusted odds both self-reported and diagnosed HDP. These associations appeared to be driven by gestational hypertension, which was significantly associated with both chemicals, as contrasted to preeclampsia, which was not. This observation may be an artifact of the lower rate of preeclampsia (2%) compared to hypertension (12%) among participants. The authors reported no associations with o,p'-DDT [55•]. Finally, Smarr et al. examined nine OC pesticides (HCB, β-HCH, γ-HCH, oxychlordane, transnonachlor, mirex, p,p'-DDT, o,p'-DDT, and p.p'-DDE) measured in preconception serum from 258 women from Texas and Michigan and did not find any of them to be associated with gestational hypertension (they did not investigate preeclampsia)

[56•]. In their analysis, they attempted to control for co-exposure to multiple chemicals by including the sum of the remaining chemicals in each class to the models for individual exposures. The difference between their results and Murray et al.'s may be a factor of sample size, but may also reflect the higher levels of pesticide exposure in the South African cohort.

Smarr et al. also considered ten *PBDE* congeners (17, 28, 47, 66, 85, 99, 100, 153, 154, 183), but found no association with gestational hypertension [56•]. Among 45 preeclamptic and 75 normotensive women recruited from three university hospitals in Tehran, Eslami et al. found total PBDE concentration (the sum of congeners 28, 47, 99, 100, 153, 154, 183, 209) increased the adjusted odds of preeclampsia (OR = 2.19 [1.39, 3.45]), but the association was attenuated when total PCB concentration was added to the model to account for co-exposure (OR = 1.53 [0.90, 2.58]). This association appeared to be driven by PBDEs 28, 47, 99, and 153, which were all significantly higher in preeclamptic women in bivariate analysis. Total PCB concentration (the sum of congeners 28, 52, 99, 101, 118, 138, 153, 180, and 187) also significantly elevated the odds of preeclampsia in adjusted models both without and with total PBDE (OR = 1.77 [1.34, 2.32] for both). This association appeared to be driven by PCBs 28, 118, 138, 153, 180, and 187 [57].

A recent study drawing on subset of 976 nulliparous participants in the Norwegian Mother and Child Cohort Study examined relations among seven *PFAS* measured in second trimester plasma samples and preeclampsia, and did not find increased risk; in fact, perfluoroundecanoic acid (PFUnDA) appeared to be protective. When the shape of the dose-response function was plotted using restricted cubic splines, it seemed that the relation between PFAS and preeclampsia may be nonlinear, with effects more likely to be detectable at higher exposure levels than were present in this study [58]. Earlier studies conducted as part of the C8 Health Project to investigate health outcomes in an Appalachian community surrounding a chemical plant that used PFAS in the manufacture of fluoropolymers found weak associations of serum perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) with preeclampsia (OR = 1.3, [0.9, 1.9] and 1.3 [1.1, 1.7], respectively) [59]. These findings are in line with other studies that have reported associations of PFAS with reduced couple fecundability [60] and decreased birth weight [61]. At this time, hypothesized mechanisms involve endocrine disruption, but laboratory data suggest that at exposure-relevant concentrations for Western populations, PFAS do not affect estrogen or androgen receptor activity, steroidogenesis [62], or levels of reproductive hormones [60].

Nonpersistent Chemicals

Unlike POPs, lead, and cadmium, which have half-lives measured in years, most nonpersistent chemicals are metabolized within hours. While cumulative exposure is not an issue, because of these chemicals' ubiquity, individuals may be chronically exposed, resulting in health effects across the life course.

BPA is being phased out of many consumer products, where it was used in the production of hard, transparent plastics. Nevertheless, it is still an ingredient in epoxy resins used to line water pipes and metal food cans, and is an ingredient in printed thermal receipt paper and dental sealants. Best known as an endocrine disruptor, BPA has been associated

with adverse reproductive outcomes in adults and prenatal exposure has been linked to negative neurobehavioral, developmental, metabolic, and respiratory effects in children. BPA has also been shown to increase the risk of obesity, type 2 diabetes, and CVD in adults [63], signaling its potential to influence HDP. Two recent nested case-control studies have examined associations between BPA and preeclampsia. Cantonwine et al.'s study was nested in a pregnancy cohort and measured BPA in urine samples from three prenatal visits. The analytic sample included 50 preeclamptic women and 432 normotensive women enrolled in the Boston arm of their study. An interquartile increase in first trimester BPA concentration was associated with increased risk of preeclampsia overall (HR = 1.53 [1.04, 2.25]), but when stratified by infant sex, only the results among female infants remained statistically significant (HR = 1.58 [1.20, 2.08]) [64•]. Unlike others, Cantonwine et al. did not exclude women with a prior diagnosis of chronic hypertension from their cases. Ye et al. analyzed BPA concentration in second-trimester serum samples from 74 preeclamptic and 99 normotensive women in Fudan, China. BPA concentration was associated with increased adjusted odds of preeclampsia overall (OR = 1.39 [1.19, 1.63]), with similar results when considering mild, severe, early onset, or late onset cases vs. healthy controls [65•]. Ye et al.'s findings were consistent with those of Cantonwine et al. even though they measured BPA in serum, which is considered less reliable than urine because of potential for contamination and contains lower concentrations of nonpersistent chemicals, increasing the risk of nondetection [66].

A number of recent studies have sought to explore the biological mechanisms by which BPA might influence placental function and lead to HDP. Several potential clues have been identified, including BPA's association with increased global methylation in placental tissue [67]; its downregulation in third trimester placental tissue of the ABCG2 transporter that protects the fetus from foreign chemicals [68]; its link to increased levels of miR-146a [69], which among many other molecules targets endothelin receptor type b, which in turn is linked to increased risk of pulmonary arterial hypertension [70]; its inhibition of trophoblast migration and invasion [71]; and its inducement of trophoblast apoptosis [72]. Of particular interest is a study by Ferguson et al. who, working in the same cohort as Cantonwine et al., examined the relation of BPA to factors that influence placental vascularization, specifically soluble fms-like tyrosine kinase-1 (sFlt-1, antiangiogenic) and placental growth factor (PlGF, angiogenic), which are measurable in maternal serum and known to be predictive of preeclampsia [73]. Urinary BPA concentration was associated with increases in both sFlt-1 and the sFlt-1 to PlGF ratio when measured concurrently at different time points in pregnancy [74•]. Our own study of the same outcome in the Generation R cohort, a population-based prospective cohort study conducted in Rotterdam, did not find first trimester BPA, BPS (an increasingly prevalent substitution chemical), or the sum of BPA, BPS, and BPF to be associated with placental angiogenic markers or weight, prenatal blood pressure, or risk of HDP. However, we did find that higher summed bisphenols were linked to higher second trimester umbilical artery pulsatility index (effect attenuated after Bonferroni correction), an indicator of elevated placental vascular resistance that is associated with HDP [75] (manuscript under review).

Phthalates are another class of ubiquitous nonpersistent chemicals. Phthalates are used to increase resiliency and flexibility in plastics, and are commonly found in vinyl flooring,

medical tubing, pill coatings, raincoats, automobiles, plastic film used to wrap food, as well as personal care products such as nail polish, soap, and shampoo, where they augment fragrances. Two studies have recently assessed the relation between phthalate metabolites and HDP. In the same publication in which they presented their BPA findings, Cantonwide et al. reported that out of nine phthalate metabolites that they measured in prenatal urine, monoethyl phthalate (MEP) and the sum of four di(2-ethylhexyl) phthalate (DEHP) metabolites were positively associated with risk of preeclampsia and, as with their BPA results, they found that the association was only statistically significant in females when they stratified by infant sex [64•]. In a prospective pregnancy study out of Cincinnati, OH, Werner et al. examined associations of phthalate concentrations measured in 369 women at two times during pregnancy with maternal blood pressure measured at multiple prenatal time points, gestational hypertension, preeclampsia, eclampsia, HELLP syndrome, and a combined HDP outcome variable. They observed that urinary mono-benzyl phthalate (MBzP) concentrations in early to mid-pregnancy were associated with increased diastolic blood pressure and increased risk of HDP, and theorized that MBzP could be interfering with spiral artery invasion, thereby increasing the risk of abnormal placental development [76]. In an analogous finding, Gao et al. observed an association between mono-2-ethylhexyl phthalate (MEHP) and reduced trophoblast invasion, reduced expression of the positive trophoblast regulator MMP-9, and increased expression of the negative trophoblast regulator TIMP-1 [77]. In parallel with their findings for BPA, Ferguson et al. reported that the total concentration of urinary DEHP metabolites was associated with decreased PlGF and increased sFlt-1/PlGF ratio [74•], suggesting that phthalates may alter placental vascular development. Our Generation R results found similar antiangiogenic effects, with associations between first trimester urinary high molecular-weight phthalates and both increased sFlt-1 and sFlt-1/PlGF ratio driven by the DEHP metabolite mono-(2-carboxymethyl)hexyl phthalate (mCMHP), although the former was no longer statistically significant after Bonferroni correction. We also found suggestive associations between various phthalates and umbilical artery pulsatility index, uterine artery resistance, notching, and placental weight, but none was statistically significant after correction for multiple comparisons (manuscript under review). As with BPA, sexually dimorphic effects have been found for phthalate exposure: in one study, placentas were thicker and rounder in male infants only [78]; in another, associations of various phthalate metabolites on candidate mRNAs selected from the placenta literature differed by sex [79].

Since the demise of most OC pesticides, use of nonpersistent *OP pesticides* has become the norm. Farming communities are particularly exposed, but levels are detectable in urban populations, as well, who are exposed to OP pesticides through fruit and vegetable consumption. The epidemiologic literature on OP pesticide use and HDP is scant, but a study just published by Shaw et al. that used birth certificate and hospital discharge data from the vast farming region of the San Joaquin Valley of California from 1998 to 2011 (> 200,000 births) found any exposure to 543 pesticides, either individually or in physicochemical groupings, between 1 month before conception to date of delivery was not associated with increased risk of preeclampsia; if anything, some chemicals appeared to be slightly protective. While this study creatively utilized records from various public agencies, including spatially referenced statewide Pesticide Use Reporting records from the California

Department of Pesticide Regulation, to extract data on exposures, outcomes, and covariates, it was vulnerable to misclassification of exposure due to reliance on residential address at delivery and the inability to assess time spent at the address. The authors acknowledge that their findings may also be influenced by early pregnancy loss, as an association between pesticides and premature fetal demise would not be detected using delivery records [80].

The majority of mechanistic research has been conducted on chlorpyrifos (CPF), an OP pesticide that has been restricted for residential use in Europe, the USA, and several other jurisdictions because of documented links between prenatal exposure and neurodevelopmental effects in children, but continues to be used agriculturally in most of the world. In a series of in vitro studies from a single lab, CPF was associated with increased expression of ABCG2; GCM1, a transcription factor involved in the control of expression of PlGF and other placenta-specific genes; and the beta subunit of human chorionic gonadotropin (ßhCG), which is produced by placental trophoblast cells [81]. JEG-3 cells exposed to CPF also showed evidence of increased oxidative and endoplasmic reticulum stress [82]. Increased stroma cell apoptosis and altered villi matrix composition, basement membrane thickness, and trophoblastic layer integrity were observed in placental explant tissue exposed to CPF [83]. Two other labs reported chlorpyrifos to be associated with increased TNFα apoptosis of placental cells: one group found suggestive mechanistic evidence of differential modulation of inflammatory cytokines in CPF-exposed cells [84], while the other noted that CPF-induced toxicity was characterized by the loss of mitochondrial potential and the appearance of nuclear fragmentation and condensation [85].

Conclusions

Recent additions to the literature on the exposure to environmental toxicants and HDP have vastly expanded the breadth of our knowledge, reinforcing recommendations by the International Federation of Gynecology and Obstetrics, the American Society for Reproductive Medicine, the American Academy of Pediatrics, and the Endocrine Society that providers counsel their pregnant patients to limit exposure to environmental toxicants [86–89]. Evidence for association is strongest for links between persistent chemicals, including lead, cadmium, OC pesticides, and PCBs, and preeclampsia, although effects are sometimes not detectable at low exposure levels. Among other heavy metals that have been investigated, arsenic does not appear to be associated with preeclampsia, but emerging evidence suggests that mercury and chromium may be of concern. PBDEs and PFAS are not strongly associated with preeclampsia, but the literature on these exposures is thin and further research is warranted. Among nonpersistent chemicals, intriguing associations between BPA and placental function and development add weight to the sometimes inconsistent findings for HDP outcomes. While some studies have shown links between phthalates and both placental and HDP outcomes, there is inconsistency among which phthalate metabolites may be responsible. More research is needed to draw conclusions regarding OP pesticides.

The recent studies profiled here begin to illuminate some of the biological mechanisms that may underlie associations between environmental toxicants and HDP, including oxidative stress, epigenetic changes, endocrine disruption, and abnormal placental vascularization.

Because these outcomes are on the pathway to HDP, it is important that more prospective epidemiologic studies that collect physiologic measures and biosamples throughout pregnancy be conducted so that the results of laboratory studies may be confirmed in vivo. Prospective studies may explore whether there are critical periods in pregnancy when environmental chemicals may have particularly deleterious effects, potentially leading to miscarriage, which may be considered as an interim outcome. Prospective studies can also better enable researchers to establish temporality of exposure; in cross-sectional studies, there is the potential for reverse causation if, for example, the biochemical profile of HDP leads to a greater mobilization of environmental toxicants from tissues where they may be stored. Some of the results described here were specific to infant sex, reinforcing that in studies of endocrine-disrupting chemicals and outcomes related to the placenta, which is partially composed of fetal tissue, potential interaction with sex must be considered. Because environmental toxicants co-occur, it is important to evaluate exposure not only to individual chemicals, but also to chemical mixtures using statistical techniques that appropriately model interactions between them. Analyses should also include models of nonlinear effects.

Finally, more studies are needed that place these observed associations in a life course context. Pregnancy does not occur in a vacuum, and a woman's preconception chemical exposures and cardiovascular risk factors may play a role in whether or not she passes the "stress test" of pregnancy [90] and whether or not she develops CVD in the years that follow. Studies that follow women from the preconception period through the postnatal period and beyond will help to identify HDP risk factors that may be present before pregnancy, potentially leading to interventions that can help prevent not only HDP but later life CVD, as well.

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