SPECIAL REVIEW

REPRODUCTIVE TOXICOLOGY

Pregnancy exposure to endocrine disrupting chemicals: implications for women’s health

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Abstract

Women are ubiquitously exposed to non-persistent endocrine disrupting chemicals (EDCs) from food contact materials and personal care products. Understanding the impacts of exposure to these chemicals on pregnancy and long-term health outcomes in women is a critical area of research that has been largely overlooked. This brief review focuses on the epidemiologic literature exploring associations of non-persistent EDCs – including phthalates, parabens, bisphenols, and triclosan – with maternal pregnancy outcomes and long-term health outcomes in women. We focus on the challenges of this research, particularly assessing non-persistent EDC exposures, aspects of study design, and statistical approaches. We conclude by reviewing the best practices for non-persistent EDC research with regards to pregnancy and women’s health. Though limited, we found some evidence indicating that exposure to non-persistent EDCs is associated with pregnancy health. However, findings from these studies have been inconsistent and require corroboration. Recent studies have also proposed that non-persistent EDC exposures in pregnancy may adversely affect postnatal maternal health. To date, only a few studies have been conducted and have only focused on postpartum weight. More research is needed in this area to inform efforts to promote optimal health across the lifespan of women.

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Introduction

As many as 86% of women will give birth at least once in their lifetime (Pew Research Center, 2018). The very acts of achieving and maintaining a pregnancy are important determinants of women’s long-term health (Rich-Edwards et al. 2014, Dassanayake et al. 2020, Walker et al. 2020). For example, pregnancy complications, including gestational diabetes mellitus (GDM) and pregnancy hypertension/preeclampsia, are associated with long-term maternal metabolic changes, such as adiposity, insulin resistance, type 2 diabetes, high blood pressure, and dyslipidemia (Rich-Edwards et al. 2014, Dassanayake et al. 2020, Walker et al. 2020). Current clinical recommendations in pregnancy generally focus on healthy pregnancy and offspring outcomes, but little is understood about modifiable lifestyle factors in pregnancy that could safeguard women from developing chronic diseases long after they deliver.

Pregnancy is a period of heightened susceptibility to environmental stressors (Boyles et al. 2021) and one modifiable lifestyle factor is exposure to endocrine disrupting chemicals (EDCs). EDCs are characterized by their ability to dysregulate endocrine pathways critical for hormonal homeostasis. Biomonitoring data of non-persistent EDCs, such as phthalates, phenols, and parabens, from the National Health and Nutrition Examination Survey (NHANES) indicate that women have ubiquitous exposure to many chemicals found in personal care products (Bellavia et al. 2019), often at higher levels than men likely due to their greater use of cosmetics and other personal care products (Calafat et al. 2010, Braun et al. 2014). These EDCs are found in lotions, cosmetics, perfumes, sunscreens, hair products, feminine hygiene products, and soaps (Table 1). In addition, some of these chemicals (e.g. phthalates and bisphenols) originate from the diet due to their use in food processing and packaging, or are found in...
Table 1  Metabolites and uses of phthalates, triclosan, bisphenol A, and their replacements.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Metabolites</th>
<th>Uses in Commerce</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEHP(b)</td>
<td>Mehp, mecpp, mehp, and mechp</td>
<td>Plasticizer used in PVC plastics, food packaging, and plastic medical tubing and bags.</td>
</tr>
<tr>
<td>DiNCH</td>
<td>MHINCH</td>
<td>Plasticizer used in PVC plastics, food packaging, and medical tubing/bags (DEHP Replacement).</td>
</tr>
<tr>
<td>Dehtp</td>
<td>Mehthp and mecctp</td>
<td>Plasticizer used in PVC plastics, food packaging, and medical tubing/bags (DEHP Replacement).</td>
</tr>
<tr>
<td>BBZP(b)</td>
<td>MBZP</td>
<td>Plasticizer used in vinyl flooring, adhesives, food packaging, synthetic leather, and toys.</td>
</tr>
<tr>
<td>Dep</td>
<td>Mep</td>
<td>Scent retainer or emollient used in personal care products (cosmetics, lotions, and perfumes). Used as a medication excipient.</td>
</tr>
<tr>
<td>DnBP and DiDIB(b)</td>
<td>MnBP and MiBP</td>
<td>Scent retainer in personal care products (cosmetics, lotions, and perfumes). Used as a medication excipient. Plasticizer found in some cellulose plastics, and adhesives.</td>
</tr>
<tr>
<td>Triclosan</td>
<td>Triclosan</td>
<td>Antimicrobial compound used in soaps, personal care products, toothpaste, kitchen utensils, clothes, and cleaning products.</td>
</tr>
<tr>
<td>Triclocarban</td>
<td>Triclocarban</td>
<td>Antimicrobial compound used in personal care and consumer products (Triclosan alternative).</td>
</tr>
<tr>
<td>Bisphenol A</td>
<td>Bpa</td>
<td>Monomer used to manufacture polycarbonate plastics, resins, food cans linings, dental fillings, and medical equipment. Developer in thermal receipts.</td>
</tr>
<tr>
<td>Bisphenol F and Bisphenol S</td>
<td>Bpf and bps</td>
<td>Monomer used to manufacture food can linings, plastics, resins, and food packaging. Used in cleaning products, industrial solvents, lacquer, varnish, and adhesives. Developer in thermal receipts. (BPA Replacements)</td>
</tr>
<tr>
<td>Parabens</td>
<td>Bp, ep, mp, and pp</td>
<td>Antibacterial compound used in medications, personal care products, and foods.</td>
</tr>
<tr>
<td>Benzophenones</td>
<td>Benzophenones 1 and 3</td>
<td>Ultraviolet light filter used in sunscreens, cosmetics, consumer product packaging, sunglasses, and sports equipment.</td>
</tr>
</tbody>
</table>

\(a\)All of these EDC metabolites are measured in urine and are either the parent compound or metabolic by-products of the parent compound.

\(b\)In the United States, the Consumer Product Safety Improvement Act of 2008 restricted the use of these phthalates in children's toys and care articles to <0.1%. *The United States Food and Drug Administration has prohibited the use of triclosan and triclocarban in hand soaps and sanitizers.

 consumer products or household furnishings, resulting in ingestion of dust and contaminated food, as well as dermal absorption.

In pregnancy, exposure to several EDCs has been associated with poor pregnancy outcomes (e.g. preterm birth) and long-term consequences for infant and child health (Karwacka et al. 2017, Philippat et al. 2017). However, several recent observational studies have identified associations between exposure to some non-persistent EDCs in pregnancy and adverse maternal outcomes, including maternal glucose disruption (James-Todd et al. 2016, 2018, Shaffer et al. 2019, Yang et al. 2021) and maternal thyroid and sex hormone concentrations in pregnancy (Johns et al. 2015). These dysregulations in pregnancy can have long-term, deleterious consequences for women's health. Yet, little is known about the contribution of EDC exposures in pregnancy for maternal health after parturition.

This review will evaluate the impacts of non-persistent EDCs (phthalates, parabens, phenols, and triclosan) on women's health, with a special focus on pregnancy as a critical window of exposure for women's long-term health. We will specifically focus on non-persistent EDCs because women may be able to modify their exposure to these chemicals through behavioral changes (e.g. changing or reducing personal care product use or dietary modifications) (Harley et al. 2016). We posit that the associations of non-persistent EDCs with women's health may be partially mediated by EDC-targeted disruptions to maternal health during pregnancy, but current limitations in study design, EDC exposure measurements, and statistical methods make it difficult to definitively conclude this. In this review, we first briefly discuss pregnancy history and women's long-term health to set the stage for pregnancy as an important view into the future health of women. Second, we discuss patterns of associations of exposure to non-persistent EDCs in pregnancy in relation to pregnancy outcomes and highlight the challenges that contribute to the difficulty in establishing a cohesive picture of these relationships. Third, we explore in more detail the limited literature on non-persistent EDC exposure in pregnancy and maternal health after pregnancy. Lastly, we provide guidance for moving this research field forward to achieve the ultimate goal of identifying pregnancy-related factors that will protect women's long-term health.

Methods

For this narrative review, we searched PubMed using keywords including (but not limited to) pregnant, EDCs, specific classes of EDCs (e.g. phthalates, bisphenol), postnatal, and postpartum. We selected epidemiologic studies that illustrated challenges or best practices in designing and interpreting the exposure–outcome relationships of interest and attempted to summarize associations by class of chemical. We included articles that
were published before January 2021. For all studies reviewed here, we only described associations that were adjusted for important confounders, including sociodemographic characteristics, lifestyle factors, and health conditions (specific example of such details can be found in Table 2).

**Pregnancy outcomes as an important view into the future health of women**

Pregnancy is a time of significant physiological change that is experienced by most women during their lifetime. This unique period can also be accompanied by health complications that offer a warning for maternal health risks and long-term outcomes. Thus, it is critical to identify interventions that prevent pregnancy complications and support women’s health in the future. Several recent reviews suggest that various pregnancy pathologies, as well as the act of being pregnant, may be a 'stress test' – in that pregnancy may serve as a first glance into potential long-term health outcomes in women (Rich-Edwards et al. 2014, Ananth 2014, Durnwald 2015, Leslie & Briggs 2016, Cunningham & LaMarca 2018, Troisi et al. 2018, Dassanayake et al. 2020). Specifically, pregnancy outcomes such as ischemic placental disease, shortened gestation/preterm birth, GDM, and pregnancy hypertensive disorders have been shown to have consistent, positive associations with later cardiovascular disease and mortality in women. Several reviews have noted associations of GDM with the subsequent development of type 2 diabetes mellitus, with the greatest risk of developing type 2 diabetes mellitus occurring within 5 years of a pregnancy complicated by GDM (Rich-Edwards et al. 2014, Dassanayake et al. 2020). Evidence also suggests that extremely shortened gestation (20–31 weeks) is associated with subsequent risk of type 2 diabetes mellitus in the 10 years after pregnancy (James-Todd et al. 2013). A recent meta-analysis noted that associations of GDM and cancer varied depending on the geographic location of study participants and the type of cancer studied, with breast cancer being the most commonly studied cancer in this context (Wang et al. 2020); although another recent meta-analysis found no overall association between gestational hypertension or preeclampsia and breast cancer (Sun et al. 2018). Together, this body of work suggests that factors that impact pregnancy outcomes in women may have lasting consequences for their health, making this a susceptible period of life (Rich-Edwards et al. 2014, Leslie & Briggs 2016).

**Non-persistent EDCs in pregnancy and maternal pregnancy health**

Non-persistent EDCs dysregulate pathways governed by hormones. Given the indispensable role of hormones in establishing and maintaining a pregnancy, there has been keen interest in the potential for non-persistent EDCs to interrupt pregnancy and fetal development. However, much of this research has considered how various maternal morbidities impact fetal or child outcomes but has not specifically addressed the consequences of exposure for the health of the mother. Recent studies have begun to address these gaps. Among epidemiological studies examining associations of non-persistent EDCs and pregnancy health outcomes, the most commonly studied pregnancy health outcome is GDM. Other important pregnancy health outcomes that have been studied in relation to non-persistent EDC exposures include preeclampsia, other pregnancy hypertensive disorders, and gestational weight gain.

**Gestational diabetes mellitus**

Recently, several epidemiological studies have explored associations between non-persistent EDCs and GDM, which reported mixed results. In relation to GDM, impaired glucose tolerance, and increased blood glucose concentrations, three studies reported positive associations with monoethyl phthalate (MEP), monobutyl phthalate (MBP), and monocarboxyoctyl phthalate (MCOP) (James-Todd et al. 2016, 2018, Shafer et al. 2019) and negative associations with monocarboxyctyl phthalate (MCOP) (Shafer et al. 2019), monoisobutyl phthalate (MiBP) (James-Todd et al. 2018), and the sum of di-2-ethylhexyl phthalate (DEHP) metabolites (James-Todd et al. 2016). MEP was the only metabolite consistently and positively associated with GDM, impaired glucose tolerance, and blood glucose concentration across these studies. However, another study reported no associations between phthalate metabolites and either GDM or impaired glucose tolerance (Shapiro et al. 2015). Studies evaluating associations of phenols and parabens with pregnancy glucose complications are similarly mixed (Shapiro et al. 2015, Fisher et al. 2018, Shapiro et al. 2018, Ouyang et al. 2019, Bellavia et al. 2019, Li et al. 2019b, Liu et al. 2019, Zhang et al. 2019, Yang et al. 2021). The interpretation and synthesis of results across studies are challenged by differences in exposure assessment and outcome definitions used to characterize pregnancy glucose homeostasis endpoints. Additional inconsistencies in findings across studies may be related to the use of single pollutant models that may produce statistically significant estimates that are the result of multiple testing.

**Preeclampsia and pregnancy hypertensive disorders**

The epidemiological literature of associations between non-persistent EDCs and preeclampsia/pregnancy hypertensive disorders is sparse. Of available studies,
Table 2: Studies of non-persistent endocrine disrupting chemical exposures during pregnancy and maternal postpartum weight gain.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cohort and location</th>
<th>Sample size</th>
<th>Chemicals measured</th>
<th>Urine samples and dilution correction</th>
<th>Analytic treatment of metabolites</th>
<th>Statistical modeling</th>
<th>Outcome</th>
<th>Covariates</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodriguez-Carmona et al. 2019</td>
<td>Early Life Exposure in Mexico to Toxicants Project, Mexico City, Mexico</td>
<td>Original subset: 250, Analyzed subset: 178</td>
<td>• MEHP</td>
<td>Collected once in each trimester, women had to contribute at least one urine sample to be included</td>
<td>Summed metabolites of parent compounds</td>
<td>Path analysis that included log-transformed phthalate metabolites concentrations across pregnancy</td>
<td>Annual weight change in kg; Weight was measured up to five times in the first year postpartum and twice during follow-up visits 5.2–10.7 years later</td>
<td>• Maternal age</td>
<td>• One log-unit increase in MCP was associated with annual weight change of 0.33 kg (95% CI: 0.09, 0.56).</td>
</tr>
<tr>
<td>Peng et al. 2020</td>
<td>Early Life Exposure to Environmental Toxicants Project, Mexico City, Mexico</td>
<td>Original subset of ELEMENT: 250, Analyzed subset: 167</td>
<td>• BPA, • MEHP, • MEOHP</td>
<td>Collected once in each trimester, women had to contribute at least one urine sample to be included</td>
<td>Summed metabolites of parent compounds</td>
<td>Mixed effects linear models that incorporated repeated measures of weight</td>
<td>Average annual rate of weight change in kg through 1 year postpartum. Weight was measured up to four times postpartum. Positive beta estimates indicate slower weight change while negative indicate faster weight change</td>
<td>• Maternal age</td>
<td>• One log-unit increase in BPA was associated with 0.68 kg/year slower weight change (95% CI: 0.07, 1.29).</td>
</tr>
<tr>
<td>Philips et al. 2020a</td>
<td>Generation R study, Rotterdam, the Netherlands</td>
<td>Original subset: 1,405, Analyzed subset: 1,192</td>
<td>• BPA, • BPS, • BPF, • Phthalic acid, • MMP</td>
<td>Collected three times during pregnancy, used early and mid-pregnancy samples only</td>
<td>Summed bisphenols (BPA, BPS, and BPF)</td>
<td>Multivariable linear models</td>
<td>Weight change (g) from pre-pregnancy to 6 years postpartum.</td>
<td>• Maternal age</td>
<td>• One log-unit increase in BPA was associated with weight increase of 0.68 kg/year slower weight change (95% CI: 0.07, 1.29).</td>
</tr>
</tbody>
</table>

BPA, BPS, BPF, Bisphenols A, F, S; DEHP, Di-2-ethylhexyl phthalate; DnBP, di-n-butyl phthalate; DNOP, di-n-octyl phthalate; MEP, monoethyl phthalate; MMP, monomethylphthalate; MOP, monocetyl phthalate; MBzP, mono-benzyl phthalate; MCPP, mono(3-carboxypropyl)phthalate; MCHP, mono-2-ethylhexyl phthalate; MHxP, mono-2-ethylhexylphthalate; MnBP/MiBP, mono-n/i-butyl phthalate; MCHpP, mono-(7-carboxy-n-heptyl) phthalate; MCMHP, mono-[(2-carboxymethyl)hexyl]phthalate; MECPP, mono-2-ethyl-5-carboxypentyl phthalate; MEHHP, mono-2-ethyl-5-hydroxyhexyl phthalate; MEOHP, mono-2-ethyl-5-oxohexyl phthalate.
bisphenol A (BPA) was most consistently associated with preeclampsia. Urinary BPA concentrations at 10 weeks gestation were associated with a 1.53-fold (95% CI: 1.04, 2.25) risk of preeclampsia (Cantonwine et al. 2016), and women with high serum concentrations of BPA at 16–20 weeks had 16.46-fold (95% CI: 5.42, 49.85) increase in odds of preeclampsia compared to women with low concentrations (Ye et al. 2017). However, serum BPA levels are subject to exogenous contaminations and are unlikely to be a useful biomarker of exposure (Calafat et al. 2013, 2015), thus it is difficult to interpret the findings from this study.

Associations between phthalate metabolites and preeclampsia are not consistent across studies. MEP, mono(3-carboxypropyl) phthalate (MCPP), and the metabolites of DEHP were associated with increased risk of preeclampsia, while MiBP was associated with a decreased risk (Cantonwine et al. 2016). However, MiBP measured in the first trimester was associated with elevated diastolic blood pressure only among women carrying male fetuses (Han et al. 2020). In another study, the butylbenzyl phthalate (BBzP) metabolite monobenzyl phthalate (MBzP) was positively associated with diastolic blood pressure throughout gestation, and was also associated with an increased risk of a combined outcome of pregnancy hypertension, preeclampsia, eclampsia, and HELLP syndrome (Werner et al. 2015). As with gestational diabetes, it is difficult to draw conclusions about these associations because of the variability in the measures used to identify pregnancy hypertensive disorders, the timing of exposure assessment, and the use of single pollutant models that may result in significant findings simply from chance. Additionally, the limited number of studies makes it difficult to discern patterns of associations.

**Gestational weight gain**

Both inadequate and excessive weight gain during pregnancy can have lasting implications for mothers and children (Oken et al. 2007, Komiariak & Peaceman 2017). Several studies have explored the associations between phthalate metabolites and gestational weight gain, also with mixed results. The phthalate metabolite MEP has been shown to be associated with gestational weight gain across multiple studies, but the direction of the association is not consistent. MEP was associated with 2.17-fold (95% CI: 0.98, 4.79) higher odds of excessive weight gain (James-Todd et al. 2016), whereas women with inadequate gestational weight gain were shown to have lower concentrations of MEP (Li et al. 2019a). Another study reported 1.18-fold (95% CI: 1.01, 1.39) higher odds of inadequate gestational weight gain with increasing low molecular weight phthalate metabolite concentrations prior to 18 weeks gestation (with MEP being the major component of the sum of low molecular weight phthalates in this study) (Philips et al. 2020b).

In addition to the common EDC-related challenges in study design that will be discussed in later sections, some of the inconsistency may be due to the variation in the associations across the outcome – such that the relationship between phthalates and gestational weight gain may differ in women with low vs high gain. This is suggested by findings that higher MEP concentrations were associated with greater BMI change at the 75th percentile of early gestational weight gain (Bellavia et al. 2017). This study also found associations of phthalate metabolites MCPP, MBzP, and sum of DEHP metabolites were associated with greater change in early pregnancy BMI among women whose BMI change was in the 50th and 75th percentiles, whereas the sum of DEHP metabolites was negatively associated with BMI change among women whose BMI change was in the 25th percentile (Bellavia et al. 2017).

Fewer studies have investigated parabens and phenols in relation to gestational weight gain. Methyl-, ethyl-, and propyl-paraben were all associated with first trimester gestational weight gain, but the association was strongest among women who were classified as overweight or obese (Wen et al. 2020). One study reported that bisphenol concentrations were generally associated with lower pregnancy weight gain. Early pregnancy (less than 18 weeks gestation) BPA concentrations (log-unit increase) were associated with 132 g lower weight gain from mid- to late-pregnancy (95% CI: −231 g, −34 g), and higher concentrations of BPA replacement bisphenol S (BPS) was associated with 261 g lower weight gain across pregnancy (95% CI: −466 g, −56 g) (Philips et al. 2020b). As with previous outcomes, the varied time frame of exposure assessment and the differences in timing of outcome ascertainment contribute to the challenges in synthesizing the results. These studies suggest that identifying a relevant window for both exposure and outcome is important for research that seeks to understand associations of non-persistent EDCs and gestational weight gain.

**Shortened gestational length**

In addition to the immediate risks associated with shortened gestation (for both mother and baby), shorter gestational length (or preterm birth) has also been associated with long-term maternal health outcomes, including greater risk of developing type 2 diabetes and cardiovascular disease (James-Todd et al. 2013, Tanz et al. 2019). The associations of pregnancy exposure to EDCs (including non-persistent EDCs) with shortened gestational length have been reviewed extensively (Marie et al. 2015, Ferguson & Chin 2017). Overall, the associations of non-persistent EDCs and shortened gestation or preterm birth are not consistent, with the exception of triclosan exposure for which most studies found no statistically significant associations with shortened gestation (Ding et al. 2017, Huo et al. 2018, Jamal et al. 2020, Khosshali et al. 2020).
Consistency of association is lacking for summed DEHP metabolites and shortened gestation, which have been associated with increased risk of preterm birth (Ferguson et al. 2014), decreased risk of shortened gestation (Chin et al. 2019), increased risk of long gestation (Adibi et al. 2009), and no association with gestation duration (Shoaí et al. 2016). The associations of BPA and parabens with shortened gestation and preterm birth are similarly conflicting. Understanding the associations of non-persistent EDCs and length of gestation endpoints may be limited by the low prevalence of preterm birth and the characterization of preterm birth as a binary variable; this may decrease the sensitivity of a study to detect an association. Alternatively, if the effects of non-persistent EDCs on gestational length are non-linear, the use of linear regression models for gestational age at birth will mischaracterize the association. Though it is possible that EDC exposure has the potential to impact maternal health by disrupting the length of gestation, substantially more research is needed to address the inconsistencies in prior studies.

**Non-persistent EDCs and maternal health after pregnancy**

Pregnancy has lasting consequences for women’s health, so there is reason to posit that chemical exposures in pregnancy will impact women long after they give birth.

**Hormonal disruption in pregnancy and women’s long-term health**

One likely mechanism behind this hypothesis is that EDC exposure in pregnancy alters maternal hormones, which impacts women’s health long after pregnancy (Fig. 1). Observational studies in pregnant women suggest that phthalates, phenols, and parabens may alter concentrations of estrogen, androgens, or both (Johns et al. 2015, Sathyanarayana et al. 2017, Aker et al. 2019), and a prospective case-control study found that higher gestational estrogen concentrations were associated with increased risk of breast cancer in mothers after 38 years of follow-up (Cohn et al. 2017). Changes in estrogens, as well as androgens, may also be implicated in cardiovascular disease and osteoporosis, which are prevalent in postmenopausal women (Lello et al. 2015); if these are caused by hormone disruption during pregnancy warrants further investigation. Data on the ability of non-persistent EDCs to bind to thyroid receptors are mixed (Zoeller 2007, Paul-Friedman et al. 2019), but observational studies suggest that these same EDCs are associated with altered maternal triiodothyronine (T3) and thyroxine (T4) concentrations (Johns et al. 2016, Romano et al. 2018, Derakhshan et al. 2019). Around 5–9% of women with a thyroid disorder in pregnancy may experience postpartum thyroiditis within the first year postpartum that can lead to permanent hypothyroidism, increasing the likelihood of fertility problems for subsequent pregnancies and more severe menopause symptoms during midlife (Kennedy et al. 2010). Altered thyroid hormone and thyroid stimulating hormone (TSH) concentrations later in life may also be associated with increased risk of cardiovascular disease, although additional studies are needed to confirm this association (Cappola et al. 2019). Similarly, thyroid hormones and TSH are involved in maintaining bone health and deviations from normal thyroid hormone concentrations, especially postmenopause, may be associated with increased risk of osteoporosis (Delitala et al. 2020). Whether non-persistent EDCs modulate thyroid receptor in pregnancy warrants further investigation.

**Pregnancy exposure to non-persistent EDCs and maternal long-term weight gain**

To date, the epidemiological evidence that exposure to non-persistent EDCs during pregnancy is associated with long-term maternal health is limited, and mainly focuses on postpartum weight change with inconclusive results (Table 2). One study found that pregnancy concentrations of the plasticizers MCPP and MBzP were associated with annual weight change (through 10 years postpartum), but in opposite directions; MCPP was associated with gains of 0.33 kg/year, whereas MBzP was associated with decreases of 0.21 kg/year (Rodríguez-Carmona et al. 2019). Another study found that BPA, total phthalic acid, low molecular weight phthalates, and high molecular weight phthalates were associated with weight gains ranging from 364 to 734 g 6 years postpartum (Philips et al. 2020a). As will be discussed later, these inconsistencies may be due to differences in timing of exposure assessment (both during pregnancy and postpartum). However, a key challenge for interpretation and synthesis of the information from these studies is the differences in how phthalate exposures were statistically analyzed; the first study approximated parent compound exposure, while the second study used total body burden of phthalates and categorized them based on molecular weight. Another recent study noted that BPA and phthalate metabolites measured across pregnancy were associated with slower weight loss through one-year postpartum, with effects ranging from 0.6 to 1.0 kg/year slower for an interquartile range change in metabolite concentration (Perng et al. 2020).

**Non-persistent EDC exposure in pregnancy and other long-term health outcomes in mothers**

We found no epidemiological studies investigating non-persistent EDC exposures during pregnancy and other...
postpartum health outcomes in women, such as heart disease or type 2 diabetes. One study estimated lifetime risk of breast cancer from exposure to non-persistent EDCs from plastic water bottles during pregnancy and found the risk to be minimal (Jeddi et al. 2016), but the literature linking pregnancy exposure to EDCs and cancer is also sparse. One review has hypothesized a link between pregnancy exposure to persistent EDCs and breast cancer (Terry et al. 2019), but the impact of pregnancy exposure to non-persistent EDCs has been insufficiently studied.

### Current limitations and best practices

Inconsistent results across studies make it difficult to determine if EDC exposure during pregnancy increases long-term chronic disease susceptibility in women. There are still considerable gaps in our knowledge of the long-term consequences of these exposures on women’s health during and after pregnancy. The study of women’s health in the context of non-persistent EDC exposures shares many challenges with other EDC-related research areas, but also has several unique considerations. It is also important to note that while the non-persistent EDCs reviewed here have been shown to have unique mechanisms of action in experimental models (Strakovsky & Schantz 2018), they are all classified as endocrine disrupting chemicals that share common exposure sources in human populations and are, therefore, more similar to each other than they are to other classes of chemicals. Therefore, the challenges described below related to study design must be addressed first before the field can move forward to addressing chemical-specific mechanistic questions using epidemiologic studies.

### Challenges in non-persistent EDCs research

As with most epidemiological studies of non-persistent EDCs, the field is challenged by the nature of the exposure. Metabolism and excretion of non-persistent EDCs is rapid, with half-lives ranging from hours to a few days (Sandborgh-Englund et al. 2006, Frederiksen et al. 2007, Vandenberg et al. 2007, Moos et al. 2016). Therefore, measurement of non-persistent chemical concentrations is highly dependent on timing (Lassen et al. 2013), with studies recommending that exposure is best characterized by obtaining and pooling samples over a period of days or weeks during periods relevant to disease etiology (Vernet et al. 2018, 2019). Alternatively, measurement-error correction techniques can be employed (e.g.
regression calibration) (Jackson-Browne et al. 2019). Several studies we noted here used single urine samples to characterize exposure, and a few studies of outcomes that occurred before birth (GDM for example) evaluated exposure in urine samples obtained after the outcome had already occurred.

Along with the need to carefully consider timing of exposure assessment, the matrix in which these chemicals are measured is important, and urine is the optimal matrix for measuring most of these chemicals (Calafat et al. 2013, 2015). Many of the studies included here evaluated chemical concentrations in urine, but a few used alternative matrices such as meconium (Baker et al. 2020), and serum (Ye et al. 2017). Serum and plasma are particularly poor choices for measuring non-persistent EDCs because of contamination from medical equipment and low/transient concentrations of the chemicals (Koch & Calafat 2009, Calafat et al. 2013). Future studies should continue to use urine biomarkers unless more appropriate biomarkers are developed.

With regards to measuring non-persistent EDC concentration in urine, adjustment for urine dilution is another important consideration. In pregnancy especially, variation in individual hydration levels can affect non-persistent EDC metabolite concentrations in urine. Without adjustment for urine dilution, hydration may confound or obscure associations of non-persistent EDC metabolite concentrations with the outcomes of interest. Some studies suggest the urinary dilution measure of specific gravity is most appropriate in pregnant women (MacPherson et al. 2018, Lee et al. 2021). Therefore, it is important to consider both the selection of the urinary dilution measure (e.g. creatinine, specific gravity) (MacPherson et al. 2018, Lee et al. 2021) and the statistical approach to adjustment (O’Brien et al. 2016).

Most studies reviewed here relied on single pollutant models or sums of related metabolites to characterize parent compound exposure. However, as discussed in the 2015 National Institute of Environmental Health Sciences workshop entitled ‘Statistical Approaches for Assessing Health Effects of Environmental Chemical Mixtures in Epidemiology Studies’, exposure to individual EDCs does not occur in isolation, and there are methods to address several questions related to exposure to chemical mixtures (Braun et al. 2016). For example, methodologies are available to isolate the effect of an individual compound, to assess the cumulative effects of compound mixtures, and to evaluate interactions between various compounds in a mixture (Braun & Gray 2017). A recent study in 130 cases of preterm birth and 352 random controls assessed whether individual phthalate metabolites or their combination were associated with gestational age at delivery (Boss et al. 2018). Authors reported that each interquartile range (IQR) increase in log- mono-2-ethyl-5-carboxypentyl phthalate (MECPP), was associated with a higher hazard ratio (HR) for preterm birth (HR: 1.2; 95% CI: 1.1, 1.3) and a 1.2% (95% CI: 0.3, 2.1) decrease in gestational age at birth. However, when an environmental risk score was calculated from weighted sum of phthalate metabolites, compared to the first quartile, being in the fourth quartile of the environmental risk score was associated with a HR for preterm birth of 1.4% (95% CI: 1.2, 1.8) and a 2.6% (95% CI: 0.8, 4.3) decrease in gestational age – suggesting that exposure to a cumulative mixture of phthalates elevated prematurity risk to a greater extent compared to the single pollutants (Boss et al. 2018). Therefore, future studies should consider evaluating non-persistent EDCs as mixtures to better model exposure in human populations.

**Challenges in study design specific to research evaluating prenatal non-persistent EDCs and pregnancy outcomes or maternal postnatal health**

As with all epidemiologic studies, valid study design is critical in research of non-persistent EDCs and women’s health outcomes, especially because there are likely periods of heightened susceptibility during pregnancy for many of the health outcomes mentioned in this review. Although there are many statistical methods for identifying periods of heightened susceptibility (Buckley et al. 2019), it is also important to develop studies that already account for the temporality of the exposure-outcome relationships within the design. Cross-sectional studies, though convenient, lack temporality of the exposure–outcome association, which is why conducting prospective cohort studies is critical. However, it can be challenging to design prospective studies as the disease latency and the critical timing of exposure are often unknown in pregnancy and long-term health. Additionally, prospective studies need to consider how exposure and other health behaviors change over time. To address this, some cohort studies developed protocols to collect multiple urine samples across pregnancy, but may miss timepoints of heightened susceptibility for an outcome, especially around the time of implantation, as women are often recruited into research after they conceive (Chin et al. 2019). This makes it challenging to evaluate associations of non-persistent EDC concentrations with early pregnancy outcomes, including implantation failure and early pregnancy loss. Preconception studies can sometimes overcome this limitation by capturing maternal non-persistent EDC concentrations during the preconception and early pregnancy windows, and several have demonstrated associations of non-persistent EDCs with early pregnancy loss (Toft et al. 2012, Messerlian et al. 2016). However, results from preconception cohorts may be difficult to generalize since women participating in these studies are often seeking fertility treatment. Unless the infertility is due to the male partner (and women are able to conceive naturally/with the use of intrauterine
insemination), results from these studies may not be generalizable to naturally conceived pregnancies.

While early pregnancy will always be difficult to capture, an important approach for addressing inconsistencies in exposure assessment is for future studies to collect exposure data across multiple gestational timepoints, especially during critical windows of heightened susceptibility to the effects of non-persistent EDC (Pacyga et al. 2021). With this approach, exposure can first be assessed in a cross-pregnancy pool, and then in more defined windows of susceptibility, if warranted. Another important consideration specifically related to evaluating exposure in pregnancy and long-term health outcomes is to capture exposure several times postnatally – including at the time of the health outcome measures. While challenging, it is critical to understand whether the EDC-outcome relationship is related to past (pregnancy) or current EDC exposure. Also potentially important, but infrequently studied, is paternal nonpersistent EDC exposure in the preconception period and its contribution to maternal health outcomes. Limited research indicates paternal non-persistent EDC concentrations may be associated with shortened gestation (Mustieles et al. 2020), but the paternal contribution has largely been overlooked for other conditions. As a result, future research may need to evaluate paternal contribution to women's health outcomes. Careful consideration of these study design challenges is necessary to move the field of non-persistent EDCs and women's health forward.

Conclusions

In this review, we noted a growing body of literature surrounding exposure to non-persistent EDCs during pregnancy and pregnancy outcomes in mothers, but it is thus far difficult to interpret. In contrast, recent studies have only begun to suggest that non-persistent EDC exposures in pregnancy adversely affect postnatal maternal health, but this is based on a limited number of studies focused on postnatal weight change. Therefore, while there is reason to posit that pregnancy exposures to non-persistent EDCs could impact women’s long-term health, we conclude that the current literature warrants substantial corroboration. To move the field forward, best practices using a sensitive-periods framework, valid epidemiological study design, and mixtures models, are needed in future research to maximize our ability to draw conclusions about the effects of non-persistent EDCs on women’s long-term health.

Declaration of interest

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Author contribution statement

D H and R S conceived the idea for this review. All authors contributed to writing and revising the manuscript and reviewing all versions prior to submission.

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