HHS Public Access

Author manuscript

Pharmacol Ther. Author manuscript; available in PMC 2023 November 01.

Published in final edited form as:

Pharmacol Ther. 2022 November ; 239: 108181. doi:10.1016/j.pharmthera.2022.108181.

Inflammation and oxidative stress as mediators of the impacts of environmental exposures on human pregnancy: Evidence from oxylipins

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Abstract

Inflammation and oxidative stress play major roles in healthy and pathological pregnancy. Environmental exposure to chemical pollutants may adversely affect maternal and fetal health in pregnancy by dysregulating these critical underlying processes of inflammation and oxidative stress. Oxylipins are bioactive lipids that play a major role in regulating inflammation and increasing lines of evidence point towards an importance in pregnancy. The biosynthetic production of oxylipins requires oxygenation of polyunsaturated fatty acids, which can occur through several well-characterized enzymatic and nonenzymatic pathways. This review describes the state of the science of epidemiologic evidence on oxylipin production in pregnancy and its association with 1) key pregnancy outcomes and 2) environmental exposures. We searched PubMed for studies of pregnancy that measured one or more oxylipin analytes during pregnancy or delivery. We evaluated oxylipin associations with three categories of adverse pregnancy outcomes, including preeclampsia, preterm birth, and fetal growth restriction, along with several categories of environmental pollutants. The majority of studies evaluated one to two oxylipins, most of which focused on oxylipins produced from nonenzymatic processes of oxidative stress. However, an increasing number of recent studies have leveraged technological advancements to profile a large number of oxylipins produced from distinct biosynthetic pathways. Although the literature indicated robust evidence that oxylipins produced via nonenzymatic pathways are associated with pregnancy outcomes and environmental exposures, evidence for enzymatically produced oxylipins showed that associations may differ between biosynthetic pathways. Along with summarizing this evidence, we review promising therapeutic options to regulate oxylipin production and provide a set of recommendations for future epidemiologic studies in these research areas. Further evidence is needed to improve our understanding of how oxylipins may

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Conflicts of Interest Statement

The authors declare that there are no conflicts of interest.

act as key biological mediators for the adverse effects of environmental pollutants on pregnancy outcomes.

Keywords

Inflammation; oxidative stress; oxylipin; eicosanoid; pregnancy; environmental exposure

1. Introduction

Regulation of inflammation and oxidative stress is an essential component of a healthy pregnancy. Natural changes in maternal inflammation during pregnancy help to ensure maintenance of both maternal and fetal health (Mor et al., 2011). However, when inflammation is dysregulated, it presents a pregnancy risk due to an array of downstream physiological consequences, including disruptions in immune function, vascular physiology, endocrine activity, and fetal development (Robinson and Klein, 2012; Ander et al., 2019). Chronic inflammation stemming from unresolved acute inflammatory responses is recognized to be an early determinant of disease risk in pregnancy for outcomes such as preeclampsia, preterm birth, and fetal growth restriction (Mor et al., 2011; Furman et al., 2019). Common clinical biomarkers such as C-reactive protein and tumor necrosis factor alpha provide an indicator of elevated systemic inflammation and have been associated with disease in pregnancy, but provide limited insight into critical upstream inflammatory processes (Furman et al., 2019). Oxylipins are a diverse class of bioactive lipids that play an important upstream role in regulating inflammation and oxidative stress (Dennis and Norris, 2015). Inflammation is physiologically mediated by oxylipins via direct effects on cells and tissues (e.g., vasoconstriction, vasodilation), along with the indirect effects posed on immune function (Esser-von Bieren, 2017). The role of certain oxylipins in normal pregnancy, particularly in the time periods near parturition, has been well characterized (Mosaad et al., 2020). However, increased understanding about the role oxylipins may play in the early origins of pregnancy disorders is needed to understand downstream effects of dysregulated inflammation.

There is also growing epidemiologic evidence that important pregnancy disorders (e.g., preeclampsia, preterm birth, fetal growth restriction) are influenced by exposure to chemical pollutants in the environment (Ferguson and Chin, 2017; Rosen et al., 2018; Kamai et al., 2019). However, the underlying biological mechanisms linking environmental chemical exposures to pregnancy outcomes are still uncertain. Dysregulated inflammation and oxidative stress are primarily driven by non-genetic factors (Brodin et al., 2015). Thus, a leading hypothesis is that inflammation and oxidative stress play a central role in mediating the effects of environmental exposures on pregnancy outcomes (Romero et al., 2007; Hantsoo et al., 2019). Improved understanding of the links between inflammation and adverse pregnancy outcomes, as well as how chemical exposures influence inflammation, may provide critical evidence to comprehensively understand and predict the downstream effects of chemical exposures.

In this state-of-the-art review (Grant and Booth, 2009), we aim to summarize evidence from recent epidemiologic studies investigating links between circulating oxylipins, maternal and fetal outcomes, and chemical exposures in pregnancy. We evaluate the hypothesis that oxylipins act as important biological mediators of the relationship between environmental exposures and pregnancy disorders. We identified studies in PubMed using a combination of search keywords for oxylipins (i.e., oxylipin, eicosanoid, or bioactive lipid, isoprostane), overall health effects (i.e., inflammation or oxidative stress), and related pregnancy outcomes (i.e., preeclampsia, preterm, gestational age, intrauterine growth restriction, or fetal growth). We restricted our search results to studies in human populations and refined results to include only studies that evaluated oxylipins in samples collected during pregnancy or delivery. Given important advances to lipidomic technologies for accurately identifying and quantifying oxylipins have occurred relatively recently (Quehenberger and Dennis, 2011), we restricted our results to studies published since 2010 to evaluate the most up-to-date evidence. First, we review studies that evaluate associations for preeclampsia, preterm birth, and fetal growth outcomes. Second, we summarize evidence from environmental epidemiology studies of pregnancy that evaluate associations with oxylipins. Third, we evaluate potential therapeutic options to modulate oxylipin production in pregnancy. Finally, we provide a set of recommendations for future epidemiologic studies to build upon this knowledge by generating translatable evidence to improve pregnancy outcomes.

2. Biosynthetic pathways of oxylipin production and connection to inflammation and oxidative stress

To contextualize the findings presented in this review, Figure 1 summarizes the major biosynthetic pathways of oxylipin production and the primary effects oxylipins along these pathways have on inflammation or oxidative stress. Oxylipins are a large class of bioactive lipids produced from the oxygenation of polyunsaturated fatty acids (PUFAs), including the primary omega-6 (i.e., linoleic acid [LA], arachidonic acid [AA]) and omega-3 (i.e., docosahexaenoic acid [DHA], and eicosapentaenoic acid [EPA]) PUFAs (Buczynski et al., 2009; Gabbs et al., 2015). The oxygenation of PUFAs to biosynthesize oxylipins can occur nonenzymatically via free radical peroxidation (Milne et al., 2015), or enzymatically by cytochrome P450 (CYP), lipoxygenase (LOX), and cyclooxygenase (COX) enzymes (Buczynski et al., 2009; Gabbs et al., 2015). Recent advances in mass spectrometry-based lipidomic technologies have provided the novel ability to identify and quantify a vast array of distinct plasma oxylipins with high resolution (Quehenberger and Dennis, 2011). The ability to distinguish oxylipins with similar molecular structures has provided a critical step forward in addressing underlying health effects, as seemingly small differences in structure between oxylipins can produce opposing inflammatory effects (Serhan, 2014; Dennis and Norris, 2015). For example, CYP epoxidation of AA produces epoxyeicosatrienoic acids (EETs), which can occur as varying regioisomers (i.e., 5,6-, 8,9-, 11,12-, or 14, 15-EETs) and have anti-inflammatory, angiogenic, and vasodilatory properties (Li et al., 2021). However, CYP hydroxylation of AA can alternatively produce 20-hydroxyeicosatetraenoic acid (HETE) that has important, and contrasting, pro-inflammatory and vasoconstrictive effects (Wu et al., 2014).

For the purposes of this review, we have categorized oxylipins based on enzymatic or nonenzymatic production to reflect processes of inflammation and oxidative stress, respectively. Nonenzymatic production of F_2-isoprostanes, particularly 8-iso-prostaglandin-$F_{2\alpha}$ (8-isoprostane), is well-recognized to reflect underlying oxidative stress (Milne et al., 2015). While circulating 8-isoprostane in humans is mostly derived from oxidative stress, it is possible for a very small proportion of 8-isoprostane to be enzymatically derived from COX metabolism (van't Erve et al., 2015). Thus, our separation of oxylipins by distinct enzymatic and nonenzymatic production pathways is an accurate, yet generalized, description of more complex and interrelated underlying processes. We organize epidemiologic evidence for oxylipins by biosynthetic pathway and by enzymatic or nonenzymatic production to accurately reflect important biological processes (Figure 1).

3. Circulating oxylipins and pregnancy outcomes

Our review of oxylipins and pregnancy outcomes focused on 17 studies of preeclampsia, 8 studies of preterm birth, and 8 studies of fetal growth (Figure 2).

3.1. Preeclampsia

Preeclampsia is a hypertensive disorder of pregnancy that presents serious risks to maternal and child health. Globally, preeclampsia remains a leading cause of maternal mortality and morbidity that impacts roughly 2% to 8% of pregnancies (Abalos et al., 2013). Over the past 30 years there has been a promising decrease in preeclampsia incidence due to improved health access and education, but a large disparity in occurrence still exists within and between countries (Wang et al., 2021b). Preeclampsia is generally defined by the onset of hypertension and excess proteinuria in pregnancy (ACOG 2020). The pathophysiological mechanisms leading to preeclampsia are multifactorial and remain largely uncertain, but robust evidence points towards a central role for dysregulated responses to inflammation and oxidative stress (Harmon et al., 2016). Epidemiologic evidence of inflammatory responses using measures of circulating oxylipins provides a promising avenue to improve understanding of underlying factors for preeclampsia. As summarized in Table 1, we identified 18 epidemiologic studies of preeclampsia and circulating oxylipins. Most studies were cross-sectional and measured only one or two individual oxylipin analytes from a single biosynthetic pathway.

Associations with enzymatic oxylipins: Several studies investigated oxylipins produced from AA by CYP enzymes (AA-CYP). A prospective case-control study conducted in the US collected repeated plasma samples and observed a positive association between total EET and dihydroxy-eicosatrienoic acid (DHET) oxylipins and preeclampsia (Herse et al., 2012). Although EET has anti-inflammatory effects, elevated EET concentrations could indicate compensatory mechanisms to address systemic inflammation. Another cross-sectional study conducted among women at delivery observed opposing associations, as preeclampsia was associated with lower plasma EET concentrations (Plenty et al., 2018). Additionally, a cross-sectional study that collected fasting samples of urine, plasma, and red blood cells in the third trimester found inverse associations between urinary DHETs and preeclampsia, while null associations were observed for plasma and red blood

cell concentrations of EETs, DHETs, and 20-HETE (Jiang et al., 2013). However, this study is difficult to compare with others as it assessed esterified oxylipins by collecting fasting samples (Jiang et al., 2013).

More consistent findings were observed between studies investigating oxylipins produced from AA by LOX (AA-LOX). Two cross-sectional case-control studies conducted in late pregnancy or at delivery both observed positive associations between preeclampsia and levels of lipoxin A_4 ($LXA_{4)}$ in cord blood serum (Dong and Yin, 2014) or maternal plasma (Perucci et al., 2016). Similar to EETs, LXA_4 has anti-inflammatory effects (Serhan, 2014), which may be upregulated to counteract pro-inflammatory processes of preeclampsia. Additionally, cross-sectional (Perucci et al., 2020) and longitudinal (Perucci et al., 2021) investigations in Brazil found a positive associations with LTB_4, a pro-inflammatory AA-LOX oxylipin. However, these studies also showed that oxylipins produced by DHA-LOX with pro-resolving properties, including resolvin D1 and maresin 1, were lower in preeclamptic than normotensive pregnancies (Perucci et al., 2020; Perucci et al., 2021). Together, these findings indicate there may be relatively consistent processes involving anti-inflammatory oxylipins produced from AA-LOX with preeclampsia.

The other enzymatically produced oxylipins findings included those biosynthesized from AA by COX (AA-COX). We identified three studies, including one case-control study that evaluated early pregnancy serum samples (Gene et al., 2011) and two cross-sectional studies were identified that collected maternal plasma samples in late pregnancy or at delivery (Roland et al., 2010; Perucci et al., 2020). The case-control study observed positive prospective associations between prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and preeclampsia (Gene et al., 2011), but associations were complicated by the fact that serum samples could have elevated ex vivo formation of prostaglandins (Rund et al., 2020). The two cross-sectional studies investigated both 6-keto-prostaglandin $F_{2\alpha}$ (6-keto-$PGF_{2\alpha}$) and thromboxane B_2 (TXB_2), which are stable indicators of the vasodilator prostacyclin (PGI_2) and vasoconstrictor TXA_2, respectively (Roland et al., 2010; Perucci et al., 2020). These studies observed preeclampsia associations in opposing directions for both oxylipins (Roland et al., 2010; Perucci et al., 2020). The conflicting, yet significant, results indicate that these important indicators of AA-COX activity should be investigated further in future studies.

Associations with 8-isoprostane: Approximately half of the studies we evaluated performed analyses of F_2-isoprostanes, which are oxylipins primarily produced from oxidative stress (i.e., the nonenzymatic peroxidation of AA). However, as previously noted, it is possible that low levels of 8-isoprostane in circulation are partially derived from COX (van ’t Erve et al., 2015). Regardless of their origin, prostaglandin-like molecules are considered to be both biomarkers and biological mediators of oxidative stress (Milne et al., 2015). Overall, most studies observed positive associations between F_2-isoprostanes and preeclampsia, particularly for 8-isoprostane (Bazavilvaso-Rodriguez et al., 2011; Hsieh et al., 2012; Bilodeau et al., 2015; Tetteh et al., 2015; Turpin et al., 2015; Ferguson et al., 2017c), although one study found a protective effect (de Sousa Rocha et al., 2015). Most of the studies we evaluated point towards early pregnancy as a particularly critical period of pregnancy for potential effects of F_2-isoprostanes on preeclampsia.

Importantly, there may also be certain phenotypes of preeclampsia that drive differences in inflammation and oxidative stress (Yagel et al., 2021). For example, the large prospective study by Ferguson et al. (2017c) observed that the association between 8-isoprostane and preeclampsia was driven by preeclamptic participants who did not deliver preterm. This finding indicated that oxidative stress plays a larger role for less severe phenotypes of preeclampsia (i.e., those with onset later in pregnancy) (Ferguson et al., 2017c). Additionally, poor placentation is typically considered a primary factor driving certain preeclampsia phenotypes (Steegers et al., 2010). Several studies have shown that placental tissue from preeclamptic pregnancies has higher concentrations of AA-CYP oxylipins compared to tissue from uncomplicated pregnancies (Pearson et al., 2010; Herse et al., 2012; Dalle Vedove et al., 2016; Plenty et al., 2018), and that differences are less apparent when examining levels in maternal plasma (Herse et al., 2012; Plenty et al., 2018). Thus, circulating oxylipin production may be less physiologically relevant to production levels in the placenta for certain preeclampsia phenotypes and these condition-specific considerations should be carefully evaluated when designing new studies.

3.2. Preterm birth

Preterm birth is broadly defined as delivering before 37 weeks of gestation (ACOG 2016). Globally, preterm birth impacts over 10% of pregnancies and is a leading cause of neonatal mortality and morbidity (Blencowe et al., 2013). Underlying risk factors for most preterm births are still uncertain, but increasing evidence supports a central role for dysregulated inflammation and oxidative stress (Cappelletti et al., 2016). Importantly, there is growing recognition that the distinct pathologies leading to preterm birth can produce disparate inflammatory conditions leading up to delivery (McElrath et al., 2008; Voltolini et al., 2013).

Oxylipins have garnered substantial clinical and scientific interest for playing a central role in parturition, which has predominately focused on the AA-COX-derived prostaglandins. Clinical administration of prostaglandins can induce uterine contractions and labor, while inhibition of prostaglandin biosynthesis can prevent or prolong labor and delivery (Alfirevic et al., 2015). Prostaglandins such as PGE_2 and $PGF_{2\alpha}$ are well recognized to play a role in parturition, as elevated levels can stimulate uterine contractions and promote cervix dilation and thinning through coordinated inflammatory responses (Olson and Ammann, 2007). However, our review highlights the expanding epidemiologic literature which suggests that preterm delivery is associated with dysregulation of a wider array of oxylipins. We identified 9 epidemiologic studies of circulating oxylipins in pregnancy and preterm birth (Table 2). Most studies had prospective study designs but were limited by the collection of a single maternal sample prior to delivery.

Associations with enzymatic oxylipins: Three studies quantified a robust set of approximately 50-80 oxylipins that fell along all major biosynthetic pathways (i.e., LA, AA, DHA, and EPA precursors with nonenzymatic or CYP, LOX, COX production). This included a case-control study by Borkowski et al. (2020) of maternal serum collected in the early second trimester (15-17 weeks). Borkowski et al. (2020) found that oxylipins from nearly all major biosynthetic pathways were positively associated overall preterm birth (Borkowski et al., 2020). However, these associations were observed almost exclusively

among women with prepregnancy obesity, had limited covariate adjustments (maternal age and race/ethnicity), and had limited sample sizes for preterm birth (n=17) (Borkowski et al., 2020). Another case-control study by Aung et al. (2019) examined a large panel of oxylipins in maternal plasma and urine collected in the late second trimester (23-28 weeks). The authors also observed positive associations between oxylipins from several biosynthetic pathways with preterm birth, particularly for oxylipins produced from AA or LA precursors by LOX enzymes (Aung et al., 2019), after accounting for several important covariates and in a sample that included a larger number of preterm births (n=58). Finally, a cross-sectional study in Sweden evaluated a large number of plasma oxylipins on women at high risk of preterm delivery who presented symptoms of delivery onset at study enrollment (Svenvik et al., 2021). Although this study found interesting associations with several biosynthetic pathways, the results are difficult to compare with other studies because preterm birth was defined as delivery before 34 weeks gestation and samples were taken at different gestational windows depending on preterm outcome (Svenvik et al., 2021).

Associations with 8-isoprostane: As with studies of preeclampsia, the majority of the research on oxylipins and preterm birth focused on associations with oxidative stress using 8-isoprostane. The strongest study design was a large case-control study that collected repeated urine samples spanning all trimesters (Ferguson et al., 2015). The authors observed positive associations between urinary 8-isoprostane and preterm birth, which were most evident among samples collected in late pregnancy (Ferguson et al., 2015). These findings were consistent with a prospective cohort study conducted in Puerto Rico, which observed 8-isoprostane, its primary metabolite, and the AA-COX produced oxylipin PGF were positively associated with preterm birth, and that associations were strongest in late pregnancy (Eick et al., 2020). Similarly, Rosen et al. (2019) observed positive associations between urinary levels of the primary metabolite of 8-isoprostane measured in late pregnancy and preterm birth, though they did not observe associations with the parent compound. Other studies that measured 8-isoprostane in plasma rather than urine, at mid-pregnancy or at delivery, found inconsistent associations with preterm birth (Hsieh et al., 2012; Mestan et al., 2012; Ilhan et al., 2015). Studies of amniotic fluid (Longini et al., 2007; Lee et al., 2008; Park et al., 2016), umbilical cord tissue (Hong et al., 2016), and placental tissue (Mitchell et al., 2016) have also had varying results.

The discrepancies in associations could be attributable to the heterogeneity in the tissue and gestational timing of sample collection. However, as with preeclampsia, heterogeneity in findings for preterm birth could also be due to distinct outcome subtypes, which were evaluated in several of the studies we evaluated (Ferguson et al., 2015; Aung et al., 2019; Rosen et al., 2019). The study of mid-pregnancy oxylipins by Aung et al. (2019) observed that associations between oxylipins and preterm birth were primarily driven by participants who experienced a spontaneous preterm birth. The study by Ferguson et al. (2015) of 8-isoprostane, which was within the same hospital-based pregnancy cohort, also observed that associations were driven by spontaneous preterm birth. However, Rosen et al. (2019) did not observe evidence of differences in associations between urinary 8-isoprostane and preterm birth by subtype. Additional investigations are needed to help determine whether certain subtypes of preterm birth are more susceptible to dysregulated oxylipin production.

3.3. Fetal growth

Fetal growth disorders are major risk factors for adverse maternal and fetal pregnancy outcomes (McCormick, 1985; Oral et al., 2001). Lower weight for gestational age at birth is associated with complications that have persistent effects across the life course (Barker, 2006). Clinical definitions of fetal growth restriction or excessive fetal growth often vary between studies, but are typically based on standardized measures of estimated fetal weight, birth weight, or other anthropometric measures (e.g., abdominal or head circumference) taken at birth or *in utero* by ultrasound (ACOG 2021). The most common measures include small for gestational age (SGA) and large for gestational age (LGA), which are generally used to describe newborns with birth weight that is $<10^{th}$ percentile or $>90^{th}$ percentile for gestational age, respectively. The primary pathological processes underlying fetal growth disorders often involve poor uterine-placental perfusion (ACOG 2021), but the etiology in most cases is still uncertain (Mandy et al., 2019). However, increasing evidence shows subclinical inflammation and oxidative stress may play a crucial role in fetal development (Ernst et al., 2011; Thompson and Al-Hasan, 2012). We identified 8 epidemiologic studies that evaluated circulating maternal oxylipins in pregnancy and fetal growth outcomes (Table 3), most of which evaluated prospective associations between oxylipins and fetal size at birth.

Associations with enzymatic oxylipins: The most comprehensive study evaluated repeated measures of oxylipins from all major biosynthetic pathways using a case-control study design of SGA cases, LGA cases, and controls (Welch et al., 2020a). Pro-inflammatory plasma oxylipins produced by the oxidation of AA by CYP (i.e., DHETs, 19-/20-HETEs) or LOX (i.e., HETEs) enzymes, as well as those produced from LA by LOX (i.e., 9-/13-hydroxy-octadecadienoic acids [HODEs]) enzymes, were higher among participants who went on to deliver SGA infants (Welch et al., 2020a). However, associations were mostly null for participants who delivered LGA infants (Welch et al., 2020a). Importantly, this study provided novel evidence of important non-linear changes in circulating oxylipin levels across pregnancy, regardless of the infant size at delivery (Welch et al., 2020a). Another case-control study conducted spot serum sampling in the late first trimester to early second trimester and found LXA_4, a pro-resolving and anti-inflammatory oxylipin produced from AA by LOX, was lower in participants who went on to delivery SGA or LGA compared to controls (Lipa et al., 2017). Additional studies are needed to confirm findings from these two initial studies, but these results support the hypothesis that abnormal fetal growth outcomes may be influenced by dysregulated enzymatic oxylipin production.

Associations with 8-isprostane: Similar to preeclampsia and preterm birth, the majority of studies we identified focused on 8-isoprostane. Overall, despite the large variability in study designs, these studies had remarkable consistency in results that showed higher 8-isoprostane in maternal circulation is associated with reduced fetal growth. Only one study conducted maternal plasma sampling across all trimesters alongside repeated *in utero* ultrasound measures of fetal growth (Ferguson et al., 2018), which may better capture true pathological abnormalities of fetal growth (ACOG 2021). This study found inverse associations between urinary 8-isoprostane and fetal growth (Ferguson et al., 2018), with

the strongest associations observed in the late second trimester and for measures of head circumference and femur length (Ferguson et al., 2018). Another study of third trimester urine samples also found that the primary metabolite of 8-isoprostane was associated with reduced size for gestational age (Arogbokun et al., 2021). Finally, Hsieh et al. (2012) showed an association between 8-isoprostane and SGA which was independent of preeclampsia status.

4. Oxylipins as biological mediators of environmental exposures in pregnancy

Environmental exposures are important risk factors for disease across the life course. Pregnancy represents a particularly critical period for the adverse effects of environmental exposures for both maternal and fetal health (Varshavsky et al., 2020). While there is growing recognition that chemical exposures play a part in a range of adverse pregnancy processes, the understanding of mechanisms connecting exposure to health outcomes remains limited. For many chemical exposures, existing evidence supports the hypothesis that dysregulated inflammation and oxidative stress processes play an important role (Kahn and Trasande, 2018). Investigating oxylipins in the continuum between environmental exposures and pregnancy outcomes may improve our understanding of the toxicity of these compounds and provide opportunities to mitigate adverse effects. We identified three general categories of environmental exposures that have been evaluated for associations with circulating oxylipins in pregnancy (Figure 3), including consumer product chemicals, heavy metals, and air pollutants, including particulate matter (PM) and polycyclic aromatic hydrocarbons (PAHs).

4.1. Consumer product chemicals

The largest proportion of studies evaluated exposure to synthetic chemicals in consumer products, including phthalates, phenols, and organophosphate esters (OPEs). Each of these classes of consumer product chemicals have the capacity to act as endocrine disruptors and are heavily used across the globe, including among pregnant populations (Woodruff et al., 2011; Zoeller et al., 2012). Additionally, higher concentrations of exposure biomarkers to these chemicals in pregnancy have been associated with preeclampsia (Rosen et al., 2018), preterm birth (Ferguson and Chin, 2017), and fetal growth (Kamai et al., 2019).

Associations with enzymatic oxylipins: Two studies of oxylipins evaluated urinary biomarkers of both phthalates and phenols within separate subsets of the same pregnancy cohort in the US (Aung et al., 2021; Welch et al., 2021). While these studies had different study designs and statistical approaches, both evaluated plasma oxylipins produced along each major enzymatic pathway. The longitudinal study by Welch et al. (2021) found that mixtures of urinary phenols measured across pregnancy were positively associated with pro-inflammatory oxylipins produced by LA-LOX (i.e., HODEs) and AA-LOX (i.e., HETEs), while mixtures of urinary phthalate biomarkers were positively associated with LA-CYP oxylipins (i.e., epoxy-octadecenoic acid [EpOME], dihydroxy-octadecenoic acid [DiHOME]). Further, this study provided novel evidence that OPE mixtures were positively associated with LA-CYP oxylipins (Welch et al., 2021). The cross-sectional

study conducted at mid-pregnancy by Aung et al. (2021) observed generally similar associations between individual oxylipins and urinary phenol or phthalate biomarkers, but found stronger associations with anti-inflammatory AA-CYP oxylipins (i.e., EETs). Together, these findings provide evidence that each chemical class may act upon specific biosynthetic pathways of oxylipin production.

Associations with 8-isoprostane: All other studies of phthalates or phenols we evaluated had a primary focus on associations with 8-isoprostane levels. Regardless of study design or approach, the studies of urinary phthalate biomarkers found positive associations with 8-isoprostane (Ferguson et al., 2014a; Holland et al., 2016; van't Erve 2019; Cathey et al., 2021). Interestingly, the study by van't Erve et al. (2019) observed that the nonenzymatic fraction of 8-isoprostane produced via oxidative stress drove most of the associations, and that participants who reported using dietary supplements high in omega-3 PUFAs had associations of lower magnitude. The studies evaluating urinary phenols or OPEs all observed positive associations with urinary 8-isoprostane (Watkins et al., 2015; Ferguson et al., 2016; Huang et al., 2017; Ingle et al., 2020). These lines of evidence for may point towards a particularly important role for consumer product chemicals at initiating nonenzymatic oxylipin production and oxidative stress.

4.2. Heavy metals

Exposure to heavy metals (e.g., arsenic, cadmium, and lead) is well recognized to influence reproductive health and children's development (Rehman et al., 2018). There is also increasing evidence that heavy metals can impair early life immune function and instigate prolonged dysregulation of inflammation and oxidative stress (Dietert, 2009; Welch et al., 2020b). However, evidence is limited regarding how oxylipins may be involved with these effects. We identified 4 studies that evaluated associations between metals and oxylipins in pregnancy.

Associations with enzymatic oxylipins: The previously mentioned study by Aung et al. (2021) found negative associations between individual metals (e.g., barium, lead) and LA-LOX oxylipins (e.g., HODE metabolite). However, associations were less consistent between statistical models that evaluated metals individually or as a mixture (Aung et al., 2021).

Associations with 8-isoprostane: Although studies focusing on 8-isoprostane found positive associations with nickel (Ashrap et al., 2021), copper (Kim et al., 2019), or arsenic (Dashner-Titus et al., 2018), heavy metals such as lead and cadmium showed poor consistency in associations with 8-isoprostane across studies. This is somewhat surprising, given that both lead and cadmium have had robust links to oxidative stress in previous studies (Patra et al., 2011). These inconsistencies may be due to differences in the distribution of metals exposures between these populations, but may also show that metals have greater relative impact on immunological processes that are independent of oxylipin production, such as redox signaling that primarily impacts proteins or DNA (Schieber and Chandel, 2014).

4.3. Air pollutants

Air pollution is a pervasive and growing threat to global public health (Cohen et al., 2017). Exposure to low levels of ambient air pollution in pregnancy is associated with a range of adverse outcomes, including preeclampsia (Yu et al., 2020), preterm birth (Hansen et al., 2006), and fetal growth restriction (Liu et al., 2007). Although air pollution is recognized to initiate a range of inflammatory reactions (Vawda et al., 2014), few studies have investigated how exposure may influence oxylipin production in pregnancy. We identified 5 studies that investigated prenatal oxylipin levels and air pollution based on exposure to particulate matter and polycyclic aromatic hydrocarbons (PAHs). Ambient airborne particulate matter is a primary indicator of air pollution and is composed of a complex mixture of small particles. PAHs are a diverse class of chemicals emitted from the combustion of a large variety of fuel sources (e.g., coal, gasoline, wood) and represent an important component of particulate matter.

Associations with enzymatic oxylipins: An air pollution study conducted in Belgium found that pro-inflammatory oxylipins measured in cord blood were higher among individuals who experienced higher environmental exposure to particulate matter with aerodynamic diameter <2.5 μm ($PM_{2.5}$) across pregnancy (Martens et al., 2017). The study observed that oxylipins produced by specific LOX isoforms, including 5-LOX and 12/15-LOX, were the primary drivers of positive associations, while mixtures of oxylipins produced by CYP or COX had null associations with $PM_{2.5}$ (Martens et al., 2017). The potentially important role of LOX-derived oxylipins in response to small, aerosolized particle exposures has also been shown in epidemiologic studies of adults (Wang et al., 2021a) and experimental studies of mice (Li et al., 2015). The previously mentioned study by Aung et al. (2021) observed positive associations between mid-pregnancy urinary metabolites of PAH exposures and LOX-produced oxylipins.

Associations with 8-isoprostane: The other studies of air pollution focused on oxylipins primarily produced by oxidative stress. Two studies of particulate matter exposure found null associations with maternal or cord blood 8-isoprostane and a related regioisomer (Ambroz et al., 2016; Maciel-Ruiz et al., 2019). However, a cross-sectional study found positive associations between maternal urinary PAHs and 8-isoprostane in samples collected at the beginning of the third trimester (Ferguson et al., 2017b). Given that particulate matter is measured in the environment and PAHs are typically measured in biospecimens like urine, divergent associations are not altogether surprising. Future studies could improve the literature by addressing what chemical components of particulate matter and PAH are driving associations with oxidative stress.

4.4. Oxylipins as mediators of associations between environmental exposures and pregnancy outcomes

An underlying hypothesis of this review is that oxylipins act as important biological mediators of the relationship between environmental exposures and pregnancy processes. Several initial studies have employed innovative study designs and statistical methods to evaluate how oxylipins may mediate the effect of environmental chemicals on pregnancy outcomes, primarily regarding preterm birth (Mustafa et al., 2015; Ferguson et al., 2017a;

Aung et al., 2020). However, it is important to note that statistical mediation analyses of epidemiologic data require strong causal assumptions that can bias associations when not met (Vanderweele, 2015). We see three key areas in which future studies can provide a better foundation to understand the likelihood that certain causal assumptions are being met within observational settings.

First, there is a critical need for additional evidence focused on the mechanisms of toxicant actionon oxylipin production in pregnancy. This includes experimental evidence focused on understanding the biological mechanisms by which specific classes of environmental exposures may differentially modulate activity of the various enzymes that biosynthesize oxylipins. Further, additional epidemiologic evidence is needed to evaluate whether certain gestational periods are most susceptible to changes in oxylipin production in response to environmental exposures. Second, future studies should evaluate how critical modifiable factors may ameliorate effects of environmental exposures on oxylipin production in pregnancy. For example, several epidemiologic studies have evaluated how dietary indicators (e.g., omega-3 supplementation, PUFAs ratios in plasma) may impact associations between exposure biomarkers and circulating oxylipin levels in pregnancy (van't Erve 2019; Welch et al., 2021). Such metrics can provide potential insights into biological mechanisms and at the same time help inform potential public health interventions. Third, future studies should carefully consider evaluating how mixtures of chemical exposures may be impacting oxylipin production in pregnancy. Although accounting for exposure mixtures can increase the cost and complexity of any epidemiologic study, it may provide much more translatable research that accounts for co-exposures to related environmental pollutants (Carlin et al., 2013). Several studies we included in our review employed innovative statistical approaches to account for chemical mixtures (Ferguson et al., 2019; Kim et al., 2019; Aung et al., 2021; Cathey et al., 2021; Welch et al., 2021). Given that some of these initial studies have shown that different classes of chemicals are differentially associated with distinct oxylipin pathways (Aung et al., 2021; Welch et al., 2021), additional evidence of pathway-specific effects is needed to better characterize expected impacts on inflammation. All of the recommended research areas we have highlighted will benefit from increased collaboration between molecular toxicologists, reproductive biologists, and epidemiologists.

5. Therapeutic options to regulate oxylipin production in pregnancy

The modulation of oxylipin production may provide a viable way to improve pregnancy health outcomes and ameliorate the effects of environmental exposures when avoiding exposure is challenging or impossible. Oxylipin production has been a longstanding target of pharmaceutical and therapeutic treatments. Many existing therapeutic interventions are aimed at resolving dysregulated inflammation by promoting or inhibiting the production of oxylipins (Panigrahy et al., 2021). The termination of pro-inflammatory processes can be promoted by a group of endogenously synthesized oxylipins called specialized pro-resolving mediators (SPMs), such as resolvins, maresins, protectins, and neuroprotectins (Serhan, 2014). However, most SPMs have not been investigated or identified in maternal circulation during pregnancy (Elliott et al., 2017). Here, we briefly review the most promising and extensively studied of these therapeutics, which include non-steroidal anti-inflammatory

drugs (NSAIDs), dietary PUFA supplementation, and soluble epoxide hydrolase (sEH) inhibitors.

5.1. NSAIDs

An increasing number of medications aim to inhibit certain enzyme families that synthesize pro-inflammatory oxylipins while promoting the action of others that produce anti-inflammatory oxylipins. A wide array of non-steroidal anti-inflammatory drugs (NSAIDs; e.g., aspirin, celecoxibs, indomethacin) inhibit specific enzymes (e.g., COX isoforms) and can be prescribed in pregnancy (Strauss et al., 2018). Short-term administration of aspirin may be one of the safest and most practical drug therapies to ameliorate dysregulated oxylipin production in pregnancy. Aspirin and its salicylate derivates trigger the production of lipoxins with pro-resolving effects that have stronger bioactivity than when naturally produced from AA by LOX (e.g., LXA_4) (Serhan, 2014). Low-dose aspirin prophylaxis is recommended for women at high risk of preeclampsia, with treatment initiation currently recommended between 12-28 weeks of gestation (ACOG 2018). However, meta-analysis results show that administration in early pregnancy (<16 weeks) is what can dramatically reduce preeclampsia risk, while later administration (≥16 weeks) may have minimal impacts (Roberge et al., 2012). This time-sensitive risk reduction suggests that aspirin's pro-resolving and anti-inflammatory effects may be aiding the implantation process when administered prior to chorionic plate formation (Lipa et al., 2017). Additional studies are needed to determine how aspirin and related NSAIDs may impact maternal inflammation processes in pregnancies without high preexisting risk of preeclampsia. Further, there is still need for improved specificity of these medications for target enzyme isoforms, which can result in fewer adverse effects and reduce risks to fetal health (Strauss et al., 2018).

5.2. Dietary PUFA and antioxidant supplementation

Dietary supplementation with long-chained PUFAs is another intensively studied, safe, and practical intervention that aims to mitigate dysregulated oxylipin production (Djuricic and Calder, 2021). Evidence for the beneficial effects of DHA, an omega-3 PUFA, on newborn cognitive development is strong enough that DHA is a required additive for infant formula in Europe (EFSA 2014). Growing evidence from randomized control trials, including demonstrable changes of oxylipin levels in maternal circulation (Ramsden et al., 2020), supports a role for omega-3 supplementation in reducing risk of adverse maternal and fetal pregnancy outcomes (e.g., preeclampsia, preterm birth and SGA) (Vinding et al., 2019). For example, a randomized control trial showed that DHA supplementation during pregnancy was associated with larger infant size (weight, length, head circumference), as well as lower risk of preterm delivery (Carlson et al., 2013). However, there is still considerable heterogeneity in results across studies that have prevented any widespread recommendations about clinical use (Saccone et al., 2016). Given the multifaceted benefits of omega-3s on maternal and fetal health (Larque et al., 2012), there is a need for future clinical studies to more thoroughly investigate whether supplementation may reduce risk of certain outcomes. Additionally, observational studies can at least address whether dietary PUFA supplementation influences associations between oxylipins and pregnancy outcomes by using objective biomarker measures, such as the ratio of plasma omega-6 to omega-3 PUFAs (Simopoulos, 2016).

Along with modulating inflammation, dietary supplementation with omega-3 PUFAs has been shown to have secondary effects on oxidative stress (Oppedisano et al., 2020; Djuricic and Calder, 2021). However, other dietary antioxidant therapeutics are important to consider, including the well-recognized antioxidants vitamins E and C (Duhig et al., 2016). Vitamin C removes free radicals in the aqueous phase and vitamin E helps to mitigate lipid peroxidation (Traber and Stevens, 2011). An early, randomized control trial with relatively small sample size (N=283) of vitamin C and E supplementation in pregnancy showed treatment reduced incidence of preeclampsia (Chappell et al., 1999). While larger subsequent randomized control trials found that vitamin supplementation may improve antioxidant capacity in treatment groups (Poston et al., 2006), the overwhelming body of evidence shows these treatments do not prevent preeclampsia regardless of high-or low-risk status (Poston et al., 2006; Villar et al., 2009; Roberts et al., 2010; Tenorio et al., 2018). Additional work is needed to determine whether certain combinations of antioxidants and PUFA supplementation could provide effective means to reduce oxidative stress the risk of pregnancy complications.

5.3. Soluble epoxide hydrolase inhibitors

Epoxygenated oxylipins produced by CYP enzymes (e.g., EETs, EpOMEs) have strong anti-inflammatory bioactivity (Dennis and Norris, 2015). The most extensively studied epoxygenated oxylipins are the AA-derived EETs. The anti-inflammatory and vasodilatory properties of EETs provide cardioprotective effects (Spector et al., 2004). However, these effects are often limited because EETs are rapidly hydrolyzed to their less-active diol forms (DHETs) by soluble epoxide hydrolases (sEH) (Dennis and Norris, 2015). This has made inhibition of sEH activity a longstanding target for pharmaceutical therapies (Imig and Hammock, 2009). Clinical and pharmaceutical studies have found promising beneficial effects of sEH inhibition on a range of cardiovascular conditions, including dysregulated inflammation and hypertensive disorders (Shen and Hammock, 2012). Further, sEH inhibition may provide benefits outside of increasing EET bioactivity. For example, the CYP subfamilies CYP2C and CYP2J that produce EETs also metabolize LA to form EpOME, which can be hydrolyzed to the corresponding diol DiHOME by epoxide hydrolases (Dennis and Norris, 2015). DiHOMEs are produced in much higher abundance throughout the body than EETs and, importantly, have opposing pro-inflammatory and vasoconstrictive effects (Figure 1) (Edin et al., 2020). Thus, carefully designed sEH inhibitors could potentially produce a range of beneficial effects by increasing the activity of anti-inflammatory oxylipins from several biosynthetic pathways (Norwood et al., 2010). It is unclear what role genetic polymorphisms may play at predisposing individuals to pregnancy complications by altering oxylipin production from CYP or sEH activity. Prior studies of preeclampsia or renovascular hypertension found null associations between pregnancy conditions and CYP or sEH polymorphisms (Bellien and Joannides, 2013). However, understanding these and other genetic polymorphisms as they relate to oxylipin activity and pregnancy outcomes may be an interesting direction for future research. While sEH activity has been minimally studied in pregnancy, increasing evidence points towards a role in pregnancy outcomes such as preeclampsia (Dalle Vedove et al., 2016; Santos et al., 2017; Sari et al., 2017). Given that few studies have investigated the physiological implications

of sEH inhibition during pregnancy (Cizkova et al., 2016), future studies of sEH activity in pregnancy and reproduction are critical.

6. Considerations for future epidemiologic studies

As we have described, there is a growing body of evidence that prenatal oxylipin concentrations are associated with key pregnancy outcomes, as well as with prevalent environmental exposures. We would like to provide some considerations for future epidemiologic studies of oxylipins in pregnancy, regardless of whether the focus is on pregnancy outcomes or environmental exposures. Our suggestions primarily focus on the need for examining oxylipins across major biosynthetic pathways and the careful consideration for gestational timing that biological samples are collected.

6.1. Expanding from evaluating single markers to panels of oxylipins

Our review identified relatively few studies that simultaneously evaluated oxylipins from several biosynthetic pathways. However, the studies that did perform such analyses provided evidence that associations with health outcomes or chemical exposures differ across biosynthetic pathways (Martens 2017, Aung 2019, Borkowski 2020, Oliveira Perucci 2020, Welch 2020a, Aung 2021, Welch 2021). This strongly emphasizes the need for future studies to prioritize the targeted quantification of oxylipins across production pathways, including expanded measurement of enzymatic and nonenzymatic pathways. For example, we did not identify any studies that investigated oxylipins produced nonenzymatically from non-AA PUFAs, such as from DHA or EPA (Milne et al., 2015). This is a limitation in the field because these products may have promising biomarker potential (Galano et al., 2015).

Quantitatively targeting a large number of oxylipins simultaneously requires newer lipidomic technologies with high resolution, most of which use liquid chromatography with tandem mass spectrometry (LC-MS/MS) (Sorgi et al., 2018). The evolution of lipidomics with these new methods has enabled simultaneously quantifying oxylipins and other bioactive lipids across many biosynthetic pathways (Quehenberger and Dennis, 2011). Many of the studies we reviewed that analyzed a single or small number of oxylipin analytes utilized other methodological approaches such as immunoassays. The enzyme-linked immunosorbent assay (ELISA) is one most common immunoassays for quantifying oxylipins due to its relatively high cost-effectiveness, easy-to-use test kits, and good sensitivity for certain analytes (e.g., 8-isoprostane) (Liakh et al., 2020). However, ELISA methods are typically limited to measuring one analyte at a time and can have poor specificity (Il'yasova et al., 2004). Alternatively, LC-MS/MS methods provide substantially higher sensitivity and specificity and can simultaneously quantify a large number of oxylipins across all major biosynthetic pathways, but require highly technical purification steps and can still have issues separating similarly structured analytes (e.g., isomers) (Liakh et al., 2020). Targeted LC-MS/MS approaches are likely the best option for accurately quantifying a large number of oxylipin analytes in human samples, but untargeted approaches may become increasingly useful for identifying potentially important, yet unstudied, bioactive lipids in pregnancy (Liakh et al., 2020).

6.2. Biospecimen collection and evaluation

While expanding the list of oxylipin analytes to target is important, the biological matrix (e.g., serum, plasma, urine) used to target each biosynthetic pathway should always be carefully considered. For example, PUFA metabolism by COX enzymes may be more rapid and localized than other enzymes, so urine may provide a more accurate matrix than plasma for COX-produced oxylipins (Wu et al., 2010). However, plasma may be most representative of underlying inflammatory processes for oxylipins produced from most other enzymatic pathways (Dennis and Norris, 2015). Inconsistencies in published associations may stem from the fact that measures of oxylipins in maternal circulation (i.e., blood or urine) may not accurately reflect dysregulated production in specific tissues relevant to a particular condition (e.g., placenta versus maternal vasculature). While circulating oxylipin production may reflect causal inflammatory processes (Dennis and Norris, 2015) and are much more feasible than tissues in human studies, tissue-specific oxylipin production may be most relevant for understanding certain physiological processes. However, uterine tissues or fluids can be invasive or infeasible to collect in large populations, so future epidemiologic studies may benefit from alternative approaches. Exosomes have been suggested as a promising alternative to identifying links between systemic oxylipin levels and production in specific reproductive tissues (Mosaad et al., 2020). However, considerable work remains to enable exosomes and related complex molecules to be applicable to most epidemiologic study designs (Condrat et al., 2021).

Key methodological details related to biospecimen analysis also must be carefully considered when interpreting results. Most studies we examined measured free oxylipins (i.e., not covalently bound into phospholipids [non-esterified]); however, some studies measured total oxylipins (i.e., both free and esterified oxylipins). Free oxylipins are generally considered to be more bioactive (Dennis and Norris, 2015), but esterified oxylipins may have some relevant bioactivity (Spector, 2009). Regardless of portion (free or total), plasma is likely the best sample matrix to evaluate circulating oxylipins in blood (Rund et al., 2020). Serum was used in a number of studies, but serum can be problematic because of large increases in the ex vivo formation of oxylipins (e.g., COX-derived prostanoids, LOX-derived HETEs) during clotting reactions that typically occur at room-temperature (Rund et al., 2020). Urinary concentrations of oxylipins, particularly prostaglandins and isoprostanes, are correlated with plasma oxylipins and are often predictive of health outcomes (Milne et al., 2015). However, urinary oxylipins do need to be interpreted cautiously as concentrations may represent production in the liver or kidney rather than via systemic production processes (Milne et al., 2015; Mitchell et al., 2018).

Study design should also consider how natural and behavioral factors may influence oxylipin levels and potentially bias associations. For example, time of day of sample collection may influence oxylipin production based on natural diurnal variation (Colas et al., 2018) or due to recent dietary patterns (Ostermann et al., 2018; Gabbs et al., 2021). This variation in oxylipin levels could potentially confound associations with environmental exposures, as time of day of sample collection has also been associated with urinary chemical concentrations (Preau et al., 2010; Ferguson et al., 2014b; Philippat and Calafat, 2021). Although it may be infeasible to collect biological samples across participants at the

same time of day, every effort should be made to at least record the time of day of sampling. This information can be valuable to perform key sensitivity analyses that address how time of day may be influencing associations. Similarly, future studies should also carefully consider whether to collect fasting or non-fasting samples and how this may influence associations with health outcomes or environmental exposures.

Free (non-esterified) oxylipins reflect the active signaling molecules and thus may be more physiologically-relevant than esterified forms for inflammatory or vasodilatory processes (Dennis and Norris, 2015). Fasting status can influence the levels of free and esterified PUFAs in circulation, but it remains unclear whether enzymatically-derived oxylipins in free or total form in circulation better represent the tissue-specific formation of oxylipins that may influence disease progression (Spector, 2009; Dennis and Norris, 2015). Recent meal intake can influence circulating levels of enzymatically-derived oxylipins (Gouveia-Figueira et al., 2015), while the nonenzymatically-derived isoprostanes are much less susceptible to postprandial changes (Gopaul et al., 2000; Kurti et al., 2017). Although there is less potential for dietary bias with isoprostanes derived from chemical oxidation, there are still important considerations regarding the sample matrix and laboratory analysis. In urine, isoprostanes can be directly excreted or metabolized to a variety of analytes (Milne et al., 2015). In plasma, isoprostanes are found in both free and esterified forms, but can have significant issues with artificial *ex vivo* formation (Milne et al., 2015). Although both urinary and plasma forms of isoprostanes can provide relevant insights into oxidative stress (Milne et al., 2015), it has been suggested that the best measurement of isoprostanes is to include total levels in plasma (free and esterified) and urine (free and metabolized) (Halliwell and Lee, 2010).

6.3. Selecting the gestational window for oxylipin measurement

Only a handful of studies used repeated sampling to investigate longitudinal changes in circulating oxylipins across pregnancy, as most used single spot sampling. Repeated sampling can provide insight into potential periods of susceptibility, but ultimately the choice of repeated versus spot sampling may be condition-specific. For example, our review showed that oxylipin production in mid to late pregnancy may be most relevant for preterm birth, thus indicating that sampling during these periods can provide relevant insights into potential mechanisms involving inflammation. However, it is possible that other conditions like preeclampsia and fetal growth restriction may be more likely to have differential oxylipin production in early pregnancy. An initial study with repeated plasma sampling has demonstrated that maternal oxylipin production may change in a non-linear pattern across pregnancy (Welch et al., 2020a). These results closely correspond to evidence from other maternal immunological processes, such as non-linear changes in the balance of T helper type (Th) 1 to Th2 response profiles (Mor et al., 2011). Thus, future studies should consider utilizing repeated sampling to account for this natural variation and better identify potential periods of susceptibility to dysregulated inflammation for the pregnancy outcome of interest.

Additionally, it is likely that periods outside of pregnancy have important implications for oxylipin production during pregnancy. Our review was focused on studies investigating oxylipin levels during pregnancy or at delivery, but evaluating oxylipin production during

preconception and postpartum periods may provide valuable insights into health processes. For example, evidence suggests that preconception inflammation and cardiometabolic factors may be important factors for maternal and fetal pregnancy outcomes (Magnussen et al., 2007; Quesada et al., 2020). Thus, additional evidence is needed to understand how oxylipin production naturally fluctuates from preconception to postpartum in order to establish potential links to adverse outcomes.

6.4. Moving towards understanding causality

The causal role played by oxylipins in disease progression is still uncertain. In this review, we have evaluated evidence for the hypothesis that circulating oxylipins represent an important indicator of underlying tissue production preceding or exacerbating disease. However, there is still uncertainty as to whether oxylipin production may cause or change as a result of disease progression, as progression may lead to compensatory alterations in oxylipin formation (Dennis and Norris, 2015). For example, Oni-Orisan et al. (2016) found that plasma EETs were positively associated with the progression of certain subtypes of coronary artery disease (CAD). This finding would seem paradoxical, as EETs have anti-inflammatory, anti-atherosclerotic, and vasodilatory properties. However, increasing EET concentrations could be a compensatory protection process that helps mitigate disease severity. The study by Oni-Orisan et al. (2016) observed that patients with the highest plasma EET levels had the best long-term outcomes, including higher EETs among patients with nonobstructive rather than obstructive CAD (Oni-Orisan et al., 2016). Similar to compensatory effects, the direction of causality between oxylipins and diseases may be difficult to ascertain. Oxylipins such as isoprostanes can be both biomarkers of disease such as poor placental perfusion, but also act to reduce placental blood flow through activation of vasoconstrictive thromboxane receptors (Milne et al., 2015). Along with experimental studies, well-designed prospective epidemiologic studies that perform longitudinal biospecimen collection can help ascertain causal roles of potential compensatory effects and directionality of associations.

7. Concluding remarks

The epidemiologic evidence accumulated over recent years has provided evidence that inflammation and oxidative stress are critical factors involved with both healthy and pathological pregnancy. Exposure to environmental pollutants during pregnancy may adversely impact pregnancy by acting upon these inflammatory and oxidative stress pathways. The bioactive effects of oxylipins and their utility as biomarkers of inflammation and oxidative stress has made them exceptional candidates for investigating these links and provide a potential avenue for future therapeutic and diagnostic approaches to improving pregnancy outcomes. Further research is needed to establish which biosynthetic pathways of oxylipin production are most relevant for distinct health processes in pregnancy, as well as how specific environmental exposures may differentially impact these pathways. Improving the standardization of study design across pregnancy studies using the recommended approaches can help improve the impact future research has on maternal-fetal health.

Acknowledgements

This work was supported by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences.

Acronyms

8-isoprostane	8-iso-prostaglandin-F2α
AA	arachidonic acid
COX	cyclooxygenase
CYP	cytochrome P450
DHA	docosahexaenoic acid
DHET	dihydroxy-eicosatrienoic acid
DiHDPA	dihydroxy-docosapentaenoic acid
DiHETE	dihydroxy-eicosatetraenoic acid
DiHOME	dihydroxy-octadecenoic acid
EET	epoxyeicosatrienoic acid
EPA	eicosapentaenoic acid
EpDPE	epoxy-docosapentaenoic acid
EpETE	epoxy-eicosatetraenoic acid
EpOME	epoxy-octadecenoic acid
HETE	hydroxyeicosatetraenoic acid
HODE	hydroxy-octadecadienoic acid
LA	linoleic acid
LGA	large for gestational age
LOX	lipoxygenase
LT	leukotriene
LX	lipoxin
PG	prostaglandin
PGI	prostacyclin
RBC	red blood cell
SGA	small for gestational age

TX	thromboxane
IUGR	intrauterine growth restriction
SGA	small for gestational age

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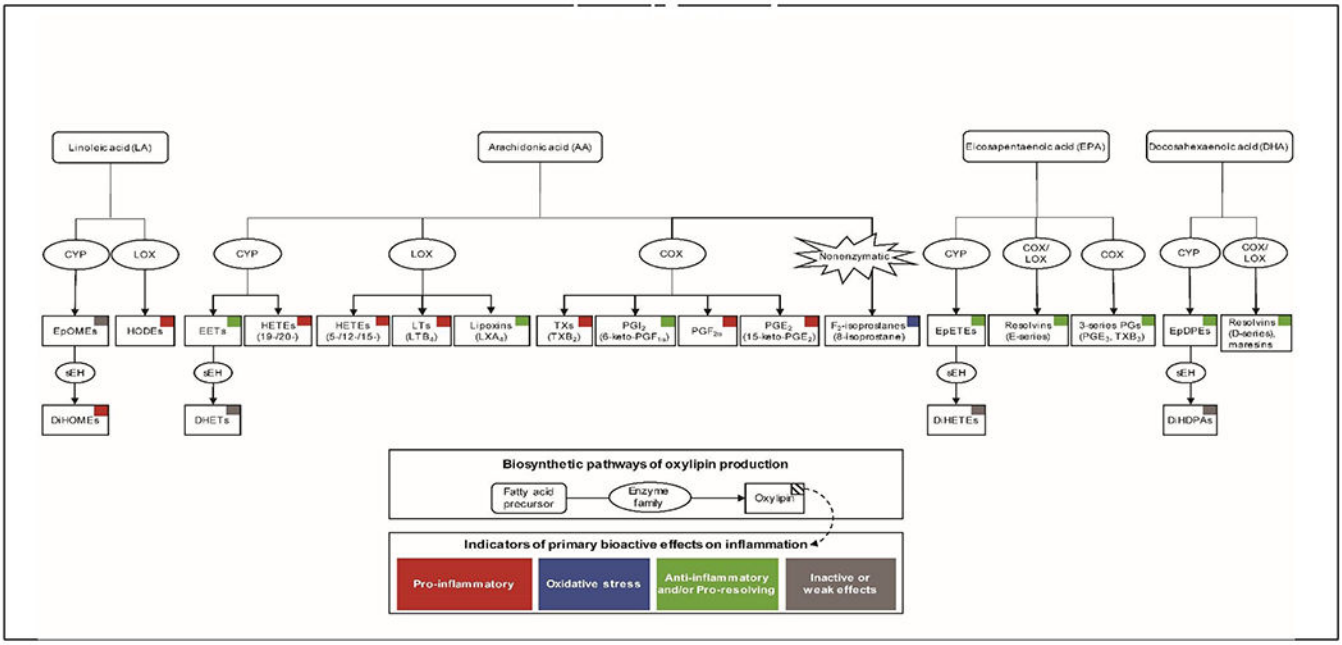
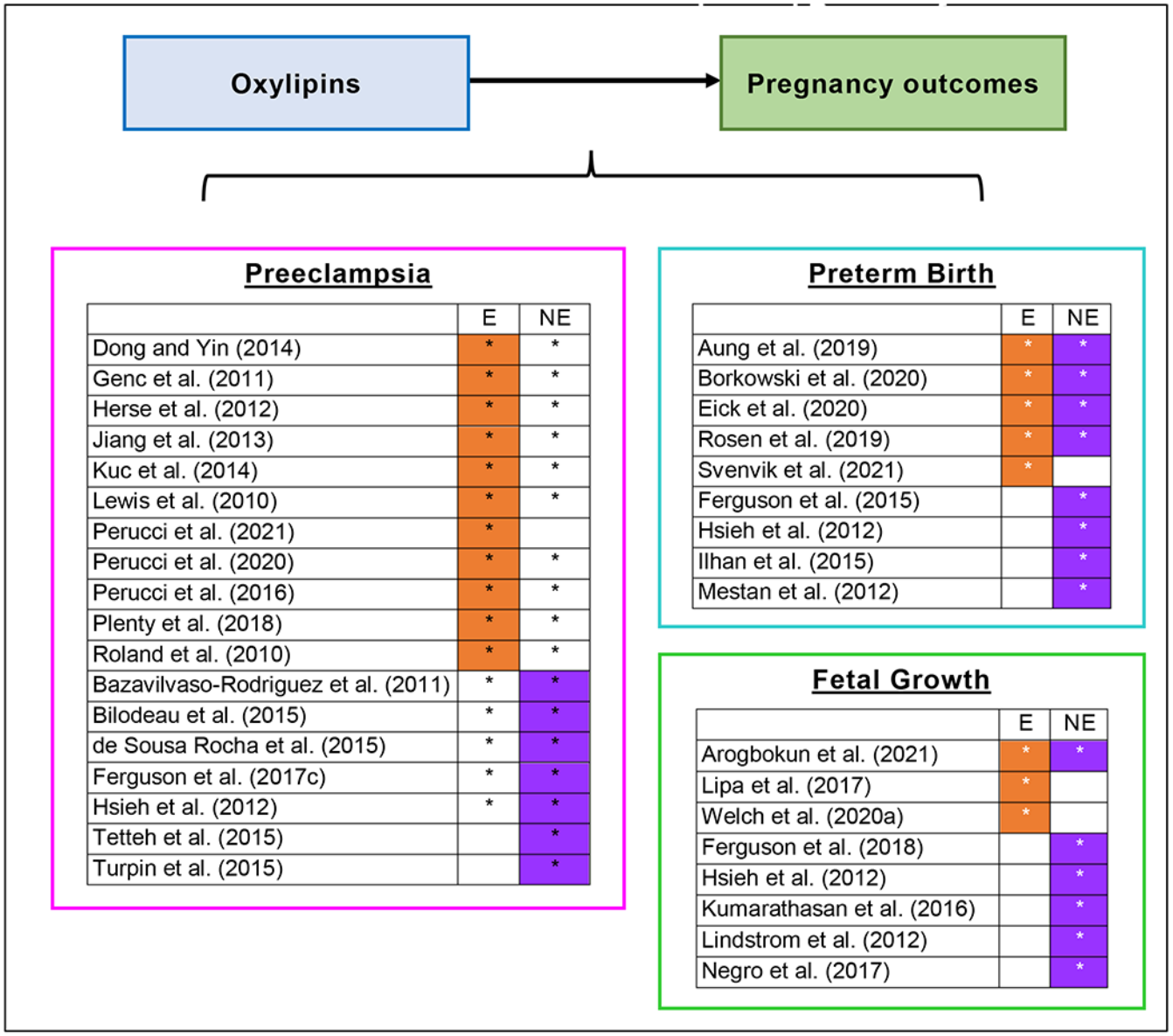


Figure 1.

Major biosynthetic pathways of oxylipin production and the bioactive effects of oxylipins on inflammation

Please note that after aspirin-acetylation, COX acts similar to 15-LOX to produce pro-resolving mediators shown (e.g., D-series resolvins, maresins) and not shown (e.g., protectins, neuroprotectins) in the figure.

Abbreviations: 8-isoprostane, 8-iso-prostaglandin-F2α; AA, arachidonic acid; COX, cyclooxygenase; CYP, cytochrome P450; DHA, docosahexaenoic acid; DHET, dihydroxy-eicosatrienoic acid; DiHDPA, dihydroxy-docosapentaenoic acid; DiHETE, dihydroxy-eicosatetraenoic acid; DiHOME, dihydroxy-octadecenoic acid; EET, epoxyeicosatrienoic acid; EPA, eicosapentaenoic acid; EpDPE, epoxy-docosapentaenoic acid; EpETE, epoxy-eicosatetraenoic acid; EpOME, epoxy-octadecenoic acid; HETE, hydroxyeicosatetraenoic acid; HODE, hydroxy-octadecadienoic acid; LA, linoleic acid; LOX, lipoxygenase; LT, leukotriene; LX, lipoxin; PG, prostaglandin; PGI, prostacyclin; TX, thromboxane



Preeclampsia	E	NE
Dong and Yin (2014)	*	*
Genc et al. (2011)	*	*
Herse et al. (2012)	*	*
Jiang et al. (2013)	*	*
Kuc et al. (2014)	*	*
Lewis et al. (2010)	*	*
Perucci et al. (2021)	*	
Perucci et al. (2020)	*	*
Perucci et al. (2016)	*	*
Plenty et al. (2018)	*	*
Roland et al. (2010)	*	*
Bazavilvaso-Rodriguez et al. (2011)	*	*
Bilodeau et al. (2015)	*	*
de Sousa Rocha et al. (2015)	*	*
Ferguson et al. (2017c)	*	*
Hsieh et al. (2012)	*	*
Tetteh et al. (2015)		*
Turpin et al. (2015)		*

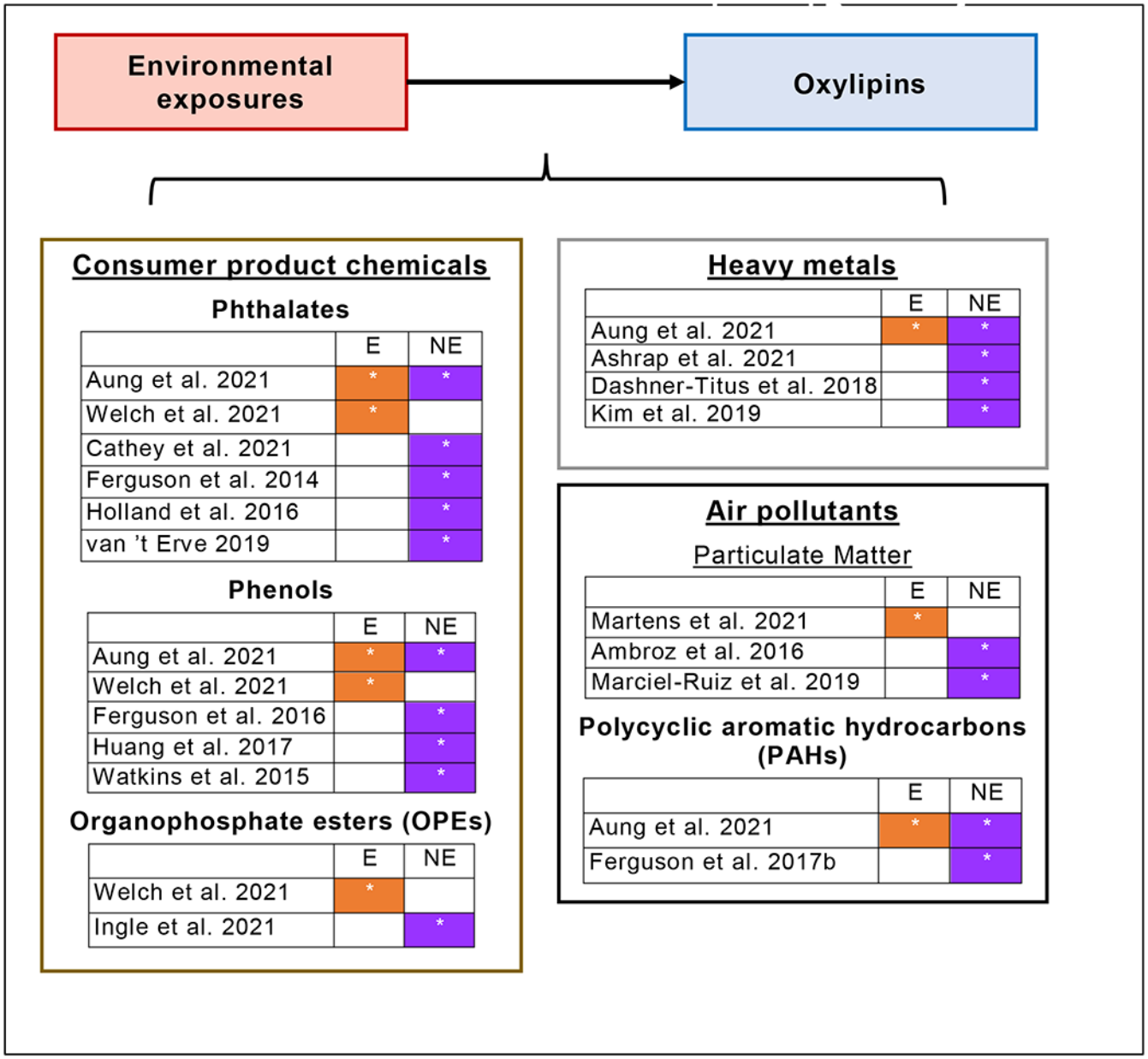
Preterm Birth	E	NE
Aung et al. (2019)	*	*
Borkowski et al. (2020)	*	*
Eick et al. (2020)	*	*
Rosen et al. (2019)	*	*
Svenvik et al. (2021)	*	
Ferguson et al. (2015)		*
Hsieh et al. (2012)		*
Ilhan et al. (2015)		*
Mestan et al. (2012)		*

Fetal Growth	E	NE
Arogbokun et al. (2021)	*	*
Lipa et al. (2017)	*	
Welch et al. (2020a)	*	
Ferguson et al. (2018)		*
Hsieh et al. (2012)		*
Kumarathasan et al. (2016)		*
Lindstrom et al. (2012)		*
Negro et al. (2017)		*

Figure 2.

Overview of epidemiologic studies investigating associations between circulating oxylipins and pregnancy outcomes

Study evaluated oxylipins produced via enzymatic (E) and/or nonenzymatic (NE) biosynthetic pathways



Phthalates	E	NE
Aung et al. 2021	*	*
Welch et al. 2021	*	
Cathey et al. 2021		*
Ferguson et al. 2014		*
Holland et al. 2016		*
van 't Erve 2019		*

Phenols	E	NE
Aung et al. 2021	*	*
Welch et al. 2021	*	
Ferguson et al. 2016		*
Huang et al. 2017		*
Watkins et al. 2015		*

Organophosphate esters (OPEs)	E	NE
Welch et al. 2021	*	
Ingle et al. 2021		*

Heavy metals	E	NE
Aung et al. 2021	*	*
Ashrap et al. 2021		*
Dashner-Titus et al. 2018		*
Kim et al. 2019		*

Particulate Matter	E	NE
Martens et al. 2021	*	
Ambroz et al. 2016		*
Marciel-Ruiz et al. 2019		*

Polycyclic aromatic hydrocarbons (PAHs)	E	NE
Aung et al. 2021	*	*
Ferguson et al. 2017b		*

Figure 3.

Overview of epidemiologic studies investigating associations between circulating oxylipins in pregnancy and environmental exposures

Study evaluated oxylipins produced via enzymatic (E) and/or nonenzymatic (NE) biosynthetic pathways.

Table 1.

Epidemiologic studies investigating associations between circulating oxylipins in pregnancy and preeclampsia (PE)

Reference[a]	Country	Study design and sample size	Timing[b]	Matrix	Pathway: Oxylipins	PE associations[c]
Dong and Yin (2014)	China	Design: Cross-sectional case-control Sample: N=90; n=60 PE	Delivery	Cord blood serum	AA-LOX: LXA_4	(+) LXA_4
Genc et al. (2011)	Turkey	Design: Prospective case-control Sample: N=45; n=21 PE	Trimesters 1-2 (2 samplings)	Serum	AA-COX: $PGF_{2\alpha}$	(+) $PGF_{2\alpha}$
Herse et al. (2012)	USA	Design: Case-control Sample: N=20; n=10 PE cases	Not reported	Plasma	AA-CYP: EETs, DHETs, 20-HETE	(+) 5,6-(EET+DHET) (+) 14,15-(EET+DHET)
Jiang et al. (2013)	Italy	Design: Cross-sectional matched case-control Sample: N=48; n=19 PE cases	Trimester 3	Urine, plasma, and RBCs	AA-CYP: EETs, DHETs, 20-HETE	(−) DHET (urine)
			Delivery	Plasma and RBC; Cord blood plasma and RBC	AA-CYP: EETs, DHETs, 20-HETE	
Kuc et al. (2014)	Netherlands	Design: Prospective case-control Sample: N=667; n=167 PE cases	Trimester 1	Serum	46 oxylipins (analytes not reported)	
Lewis et al. (2010)	USA	Design: Cross-sectional case-control Sample: N=80; n=40 PE	Delivery	Plasma	AA-COX: 6-keto-$PGF_{1\alpha}$, TXB_2	(−) 6-keto-$PGF_{1\alpha}$ (−) ratio 6-keto-$PGF_{1\alpha}$:TXB_2
(Perucci et al., 2021)	Brazil	Design: Prospective Sample: N=28, n=11 PE cases	Trimesters 1-3 (3 samplings)	Plasma	AA-LOX: LTB_4, LXA_4, DHA-LOX: resolvin D1	(+) LTB_4 (−) resolvin D1
Perucci et al. (2020)	Brazil	Design: Cross-sectional matched case-control Sample: N=41; n=21 PE	Trimester 3	Plasma	AA-LOX: LTB_4 DHA-LOX: resolvin D1, maresin 1	(+) LTB_4 (−) resolvin D1 (−) ratio resolvin D1:LTB_4 (−) ratio maresin 1:LTB_4
Perucci et al. (2016)	Brazil	Design: Cross-sectional case-control Sample: N=76, n=27 PE cases	Trimester 3	Plasma	AA-LOX: LXA_4	(+) LXA_4
Plenty et al. (2018)	USA	Design: Cross-sectional case-control Sample: N=18; n=9 PE cases	Delivery	Plasma	AA-CYP: EETs, 20-HETE	(−) EET (+) ratio 20-HETE:total EET
Roland et al. (2010)	Canada	Design: Cross-sectional case-control Sample: N=59; n=29 PE	Delivery	Plasma	AA-COX: 6-keto-$PGF_{1\alpha}$, TXB_2	(+) 6-keto-$PGF_{1\alpha}$ (−) TXB_2 (+) ratio 6-keto-$PGF_{1\alpha}$:TXB_2
Bazavilvaso-Rodriguez et al. (2011)	Mexico	Design: Cross-sectional case-control Sample: N=45; n=20 PE	Trimester 3	Serum	AA-nonenzymatic: 8-isoprostane	(+) 8-isoprostane
Bilodeau et al. (2015)	Canada	Design: Prospective case-control Sample: N=93; n=33 PE	Trimesters 1-2	Plasma	AA-nonenzymatic: Class III F_2-isoprostane regioisomers (8-isoprostane, 8-iso-15-$PGF_{2\alpha}$); Class VI F_2-isoprostane isomer sums (5-iso-$PGF_{2\alpha}$-VI)	(+) Class VI F_2-isoprostanes

Reference[a]	Country	Study design and sample size	Timing[b]	Matrix	Pathway: Oxylipins	PE associations[c]
de Sousa Rocha et al. (2015)	Brazil	Design: Cross-sectional matched case-control Sample: N=36; n=18 PE	Trimester 3	Urine (24-hr sampling)	AA-nonenzymatic: 8-isoprostane	(−) 8-isoprostane
Ferguson et al. (2017c)	USA	Design: Prospective cohort Sample: N=441; n=50	Trimesters 1-3 (4 samplings)	Urine	AA-nonenzymatic: 8-isoprostane	(+) 8-isoprostane
Hsieh et al. (2012)	Taiwan	Design: Cross-sectional cohort Sample: N=503; n=10 PE	Trimester 2	Plasma	AA-nonenzymatic: 8-isoprostane	(+) 8-isoprostane
Tetteh et al. (2015)	Ghana	Design: Cross-sectional case-control Sample: N=102 PE (early vs late onset)	Trimester 3	Urine	AA-nonenzymatic: 8-isoprostane	(+) 8-isoprostane (early vs late PE)
Turpin et al. (2015)	Ghana	Design: Cross-sectional matched case-control Sample: N=150; n=50 PE	Trimester 2	Plasma	AA-nonenzymatic: 8-isoprostane	(+) 8-isoprostane

Abbreviations: (−), negative association; (+), positive association; 8-isoprostane, 8-iso-prostaglandin-F2α; AA, arachidonic acid; COX, cyclooxygenase; CYP, cytochrome P450; DHA, docosahexaenoic acid; DHET, dihydroxy-eicosatrienoic acid; EET, epoxyeicosatrienoic acid; HETE, hydroxyeicosatetraenoic acid; LOX, lipoxygenase; LT, leukotriene; LX, lipoxin; PG, prostaglandin; RBC, red blood cell; TX, thromboxane

[a]Reference studies were identified in PubMed using a multi-stage approach. First, the following search phrase was used to identify an initial list of human studies published since 2010: (preeclampsia) AND (oxylipin OR eicosanoid OR bioactive lipid OR isoprostane) AND (inflammation OR oxidative stress) AND (2010/1/1:2022/02/01 [pdat]) AND (humans[Filter]) AND (english[Filter]) NOT (review[Filter] OR systematicreview[Filter]). This search produced 54 results, which were then paired down to the 18 reviewed studies of fetal growth after excluding duplicates and reviewing articles for relevant areas of focus.

[b]Single spot sample collected unless otherwise noted

[c]Null associations left blank

Table 2.

Epidemiologic studies investigating associations between circulating oxylipins in pregnancy and preterm birth (PTB)

Reference[a]	Country	Study design and sample size	Timing[b]	Matrix	Oxylipins measured	PTB associations[c]
Aung et al. (2019)	USA	Design: Prospective case-control Sample: N=173; n=58 PTB (spontaneous, placental)	Trimester 2	Plasma, urine	48 oxylipins in plasma (all major enzymatic pathways) AA-nonenzymatic: 8-isoprostane (urine, total)	(+) LA-CYP/LOX (+/−) AA-CYP (+) AA-LOX/COX (+) 8-isoprostane
Borkowski et al. (2020)	USA	Design: Prospective matched case-control Sample: N=102; n=51 PTB (<31 weeks)	Trimester 2	Serum	82 oxylipins (all major enzymatic pathways; AA- nonenzymatic pathway)	(+) AA-CYP/LOX/COX oxylipins (+) LA-CYP/LOX oxylipins (+) F2-isoprostanes
Eick et al. (2020)	Puerto Rico	Design: Prospective Sample: N=469, n=50 PTB	Trimesters 2-3 (3 samplings)	Urine	AA-COX: $PGF_{2\alpha}$ AA-nonenzymatic: 8-isoprostane (free), 8-isoprostane metabolite	(+) 8-isoprostane (+) 8-isoprostane metabolite (+) $PGF_{2\alpha}$
Rosen et al. (2019)	USA	Design: Prospective Sample: N=740; n=61 PTB (overall, spontaneous)	Trimester 3	Urine	AA-COX: $PGF_{2\alpha}$ AA-nonenzymatic: 8-isoprostane (free), 8-isoprostane metabolite	(+) 8-isoprostane metabolite
(Svenvik et al., 2021)	Sweden	Design: Cross-sectional (PTB-only) Sample: N=80; n=21 PTB (<34 weeks)	Delivery or Trimester 3	Plasma	67 oxylipins (all major enzymatic pathways)	(−) 9,10-DiHOME (LA-LOX) and 9,10-DiHODEs (αLA-LOX) (+) 8-HETE (AA-LOX)
Ferguson et al. (2015)	USA	Design: Prospective case-control Sample: N=482; n=130 PTB (spontaneous, placental)	Trimesters 1-3 (4 samplings)	Urine	AA-nonenzymatic: 8-isoprostane (total)	(+) 8-isoprostane
Hsieh et al. (2012)	Taiwan	Design: Prospective Sample: N=503; n=17 PTB	Trimester 2	Plasma	AA-nonenzymatic: 8-isoprostane	
Ilhan et al. (2015)	Turkey	Design: Cross-sectional matched case-control Sample: N=72*, n=34 PTB *	Delivery	Plasma	AA-nonenzymatic: 8-isoprostane	(−) 8-isoprostane
Mestan et al. (2012)	USA	Design: Cross-sectional Sample: N=237 PTB (≤28, 29-33, and <37 weeks)	Delivery	Cord blood plasma	AA-nonenzymatic: 8-isoprostane	(+) 8-isoprostane (early vs late PTB)

Abbreviations: 8-isoprostane, 8-iso-prostaglandin-F2α; AA, arachidonic acid; COX, cyclooxygenase; CYP, cytochrome P450; LA, linoleic acid; LOX, lipoxygenase; PG, prostaglandin

[a] Reference studies were identified in PubMed using a multi-stage approach. First, the following search phrase was used to identify an initial list of human studies published since 2010: (preterm OR gestational age) AND (oxylipin OR eicosanoid OR bioactive lipid OR isoprostane) AND (inflammation OR oxidative stress) AND (2010/1/1:2022/02/01[pdat]) AND (humans[Filter]) AND (english[Filter]) NOT (review[Filter] OR systematicreview[Filter]). This search produced 145 results, which were then paired down to the 9 reviewed studies of preterm birth after excluding duplicates and reviewing articles for relevant areas of focus.

[b] Single spot sample collected unless otherwise noted

[c] Null associations left blank

Table 3.

Epidemiologic studies investigating associations between circulating oxylipins in pregnancy and fetal growth

Reference[a]	Country	Growth measure outcomes	Study design and sample size	Sample timing[b]	Sample Matrix	Oxylipins measured	Fetal growth association[c]
Arogbokun et al. (2021)	USA	Birth weight for gestational age (sex specific)	Design: Prospective Sample: N=736	Trimester 3	Urine	AA-COX: $PGF_{2\alpha}$ AA-nonenzymatic: 8-isoprostane (free), 8-isoprostane metabolite	Birth weight:(−) 8-isoprostane and metabolite
Lipa et al. (2017)	Poland	SGA (≤10th percentile for gestational age) LGA (≥90th percentile for gestational age)	Design: Prospective case-control Sample: N=185; n=19 SGA; n=32 LGA	Trimester 1-2	Serum	AA-LOX: LXA_4	SGA and LGA: (−) LXA_4
Welch et al. (2020a)	USA	SGA (≤10th percentile for gestational age) LGA (≥90th percentile for gestational age)	Design: Prospective matched case-control Sample: N=90; n=31 SGA; n=28 LGA	Trimesters 1-3 (3 samplings)	Plasma	57 oxylipins (all major enzymatic pathways)	SGA: (+) LA-LOX (9- & 13-HODE) (+) AA-CYP (DHETs, 19- & 20-HETE) (+) AA-LOX (5-, 8-, 12-, & 15-HETE)
Ferguson et al. (2018)	USA	Ultrasound: head circumference, abdominal circumference, femur length, estimated fetal weight Delivery: birthweight for gestational age	Design: Prospective Sample: N=482	Trimesters 1-3 (4 samplings)	Urine	AA-nonenzymatic: 8-isoprostane (total)	Birth weight: (−) 8-isoprostane Head and femur circumference (ultrasound): (−) 8-isoprostane
Hsieh et al. (2012)	Taiwan	SGA (≤10th percentile for gestational age and sex)	Design: Prospective Sample: N=503; n=40 SGA	Trimester 2	Plasma	AA-nonenzymatic: 8-isoprostane	SGA: (+) 8-isoprostane
Kumarathasan et al. (2016)	Canada	Birth weight (categorical quantiles at <25th, 25-75th, >75th)	Design: Prospective Sample: N=144	Trimester 3	Plasma	AA-nonenzymatic: 8-isoprostane	Birth weight (<25th percentile): (−) 8-isoprostane
Lindstrom et al. (2012)	Bangladesh	Low birth weight (<2500 g), low birth length (lowest tertile), small birth head (lowest tertile), small birth chest circumference (lowest tertile)	Design: Prospective Sample: N=374	Trimester 2-3 (2 samplings)	Urine	AA-nonenzymatic: 8-isoprostane	Low birth weight, small length, small chest circumference LBW, small birth length, small birth chest circumference: (+) 8-isoprostane (middle tertile)
Negro et al. (2017)	Italy	SGA LGA	Design: Cross-sectional matched case-control Sample: N=245	Delivery	Cord blood plasma	AA-nonenzymatic: 8-isoprostane	SGA: (+) 8-isoprostane

Abbreviations: 8-isoprostane, 8-iso-prostaglandin-F2α; AA, arachidonic acid; COX, cyclooxygenase; CYP, cytochrome P450; DHET, dihydroxy-eicosatrienoic acid; HETE, hydroxyeicosatetraenoic acid; HODE, hydroxy-octadecadienoic acid; LGA, large for gestational age; LOX, lipoxygenase; LX, lipoxin; SGA, small for gestational age

[a]Reference studies were identified in PubMed using a multi-stage approach. First, the following search phrase was used to identify an initial list of human studies published since 2010: (IUGR OR fetal growth OR SGA) AND (oxylipin OR eicosanoid OR bioactive lipid OR isoprostane) AND (inflammation OR oxidative stress) AND (2010/1/1:2022/02/01 [pdat]) AND (humans[Filter]) AND

(english[Filter]) NOT (review[Filter] OR systematicreview[Filter]). This search produced 78 results, which were then paired down to the 8 reviewed studies of fetal growth after excluding duplicates and reviewing articles for relevant areas of focus.

[b] Single spot sample collected unless otherwise noted

[c] Null associations left blank