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Urinary oxidative stress biomarkers are associated with preterm birth: an ECHO program study

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Abstract

Background: Preterm birth is the leading cause of infant morbidity and mortality worldwide. Elevated levels of oxidative stress have been associated with an increased risk of delivering preterm. However, most studies testing this hypothesis have been conducted in racially and demographically homogenous study populations, which do not reflect the diversity within the United States.

Objective: We leveraged four cohorts participating in the Environmental influences on Child Health Outcomes Program to conduct the largest study to date examining biomarkers of oxidative stress and preterm birth (N=1,916). We hypothesized that elevated oxidative stress would be associated with higher odds of preterm birth, particularly preterm birth of spontaneous origin.

Study Design: We conducted a pooled and meta-analysis of four birth cohorts spanning multiple geographic regions in the mainland United States and Puerto Rico (N=208 preterm births; N=1,708 full-term births). 8-iso-prostaglandin-F_{2α}, 2,3-dinor-5,6-dihydro-8-iso-prostaglandin-F_{2α} (F₂-IsoP-M; the major 8-iso-prostaglandin-F_{2α} metabolite), and prostaglandin-F_{2α} were measured in urine samples obtained during the second and third trimesters. Logistic regression was used to calculate adjusted odds ratios and 95% confidence intervals for the associations between averaged biomarker concentrations for each participant and all preterm births, spontaneous preterm births, non-spontaneous preterm births (births of medically indicated or unknown origin), and categories of preterm birth (early, moderate, late). Individual oxidative stress biomarkers were examined in separate models.

Results: Approximately 11% of our analytic sample was born preterm. Relative to full-term births, an interquartile range increase in averaged concentrations of F₂-IsoP-M was associated with higher odds of all preterm births (odds ratio=1.29, 95% confidence interval=1.11, 1.51), with a stronger association observed for spontaneous preterm birth (odds ratio= 1.47, 95% confidence interval=1.16, 1.90). An interquartile range increase in averaged concentrations of 8-iso-prostaglandin-F_{2α} was similarly associated with higher odds of all preterm births (odds ratio=1.19, 95% confidence interval=0.94, 1.50). The results from our meta-analysis were similar to those from the pooled combined cohort analysis.

Conclusions: We observed that oxidative stress, as measured by 8-iso-prostaglandin-F_{2α}, F₂-IsoP-M, and prostaglandin-F_{2α} in urine, was associated with increased odds of preterm birth, particularly preterm birth of spontaneous origin and delivery prior to 34 completed weeks of gestation.

Condensation:

Among 1,916 pregnant people in the United States, we observed that elevated oxidative stress was associated with increased odds of preterm birth.

Keywords

isoprostanes; preterm birth; oxidative stress; adverse pregnancy outcomes; preterm labor; preterm PROM; spontaneous preterm birth; 8-iso-prostaglandin-F_{2α}; prostaglandin F_{2α}; F₂-IsoP-M; oxylipins; lipid peroxidation

INTRODUCTION

Oxidative stress, defined as an imbalance between the body's antioxidant system and reactive oxygen species (ROS), has been identified as a key mechanistic pathway linking chemical and non-chemical stress exposures to adverse pregnancy outcomes, including preterm birth (PTB).¹ Disease states such as preterm labor, preeclampsia, and preterm premature rupture of the membranes (PROM), may in part be caused by the release of ROS and other mediators in the placenta,²⁻⁸ which can exert immune effects and contribute to a heightened inflammatory state during pregnancy.⁹ Intravascular inflammation is also a mechanism of disease in preeclampsia, fetal growth restriction, chorioamnionitis, preterm labor and preterm PROM.¹⁰⁻¹² These inflammatory processes, as well as an increase in inflammatory cytokines, can trigger oxidative stress,¹³ highlighting that oxidative stress and inflammation are closely tied, and regulation of both is necessary for a healthy pregnancy.

Studies in pregnant and non-pregnant populations find that oxidative stress levels are associated with biological, behavioral, and social factors reflecting socioeconomic disadvantage, and are elevated in response to environmental chemical and psychosocial stress exposures.^{1-14,20} Oxidative stress biomarkers are stable throughout the day, are excreted in urine and easily detected using mass-spectrometry. Of these, F₂-isoprostanes (F₂-IsoPs) are considered to be the 'gold standard' indicators of lipid peroxidation, and reflect different biologic process compared to other oxidative stress biomarkers, such as 8-hydroxyguanosine, which reflects oxidative DNA damage, and 3-nitrotyrosine, 3-chlorotyrosine, and o,o'-dityrosine which reflect protein oxidation. F₂-IsoPs are formed from the *non-enzymatic* free radical oxidation of arachidonic acid, and have been identified as excellent biomarkers of endogenous oxidative stress.²¹⁻²⁵ Numerous F₂-IsoP isomers can be generated during this oxidative process (Figure 1). 8-iso-prostaglandin-F_{2α} (8-iso-PGF_{2α}) is formed in abundance and is the most commonly quantified F₂-IsoP in biological samples. Elevated levels of 8-iso-PGF_{2α}, particularly those measured during mid-pregnancy, are associated with higher odds of delivering preterm.²⁻²⁶⁻³¹ Importantly, 8-iso-PGF_{2α} differs from prostaglandin-F_{2α} (PGF_{2α}), a product of the *enzymatic* oxidation of arachidonic acid via cyclooxygenase (COX-1 and COX-2),³² only by the stereochemistry at carbon-8. PGF_{2α} may also independently increase the risk of PTB, as PGF_{2α} is part of the inflammatory response and stimulates uterine contractions, leading to spontaneous labor.³³⁻³⁴ In addition to F₂-IsoPs, other enzymatically produced oxylipins, including those biosynthesized from arachidonic acid via cyclooxygenase, lipoxygenase, and cytochrome p450s have been associated with adverse pregnancy outcomes, including overall and spontaneous PTB, fetal growth restriction, and preeclampsia.¹

Studies suggest that 8-iso-PGF_{2α} is not exclusively formed from non-enzymatic lipid peroxidation; it can also be generated as a side product of arachidonic acid oxidation via COX. We can distinguish the portion of 8-iso-PGF_{2α} that is generated from *non-enzymatic* (or chemical) vs. *enzymatic* (or inflammatory) oxidation using the ratio of 8-iso-PGF_{2α} to PGF_{2α}.³⁵ In addition to quantification of 8-iso-PGF_{2α} and PGF_{2α}, quantification of the major urinary metabolite of 8-iso-PGF_{2α}, 2,3-dinor-5,6-dihydro-8-iso-PGF_{2α} (F₂-IsoP-M), yields further insight into the endogenous formation of this biomolecule. F₂-IsoP-M may be a more sensitive biomarker than its parent compound when measured in urine, as it is

not subject to autoxidation and renal production.³⁶ Prior work has additionally shown that higher concentrations of F₂-IsoP-M are associated with higher odds of spontaneous PTB.³⁷

In the present study, we leveraged data from four U.S. birth cohorts with detailed information on gestational age and perinatal outcomes to test the hypothesis that elevated oxidative stress biomarkers would be associated with higher odds of PTB, specifically spontaneous PTB. A better understanding of these different pathways may aid in identifying high-risk populations and thus help in planning targeted interventions. Our analytic sample, comprised of nearly 2,000 births from racially and ethnically diverse study populations, addresses important gaps in the literature related to: (1) diversity, (2) timing and type of PTB, and (3) small sample size.

MATERIALS AND METHODS

Study Population

Our study population included four cohorts participating in the National Institutes of Health Environmental influences on Child Health Outcomes (ECHO) consortium: Chemicals in Our Bodies (CIOB– San Francisco, CA),³⁸ Illinois Kids Development Study (IKIDS– Champaign-Urbana, IL),³⁸ Puerto Rico Testsite for Exploring Contamination Threats (PROTECT),³⁹ and The Infant Development and Environment Study (TIDES – San Francisco, CA, Rochester, NY, Seattle, WA, and Minneapolis, MN).⁴⁰ Detailed information regarding study recruitment, data collection and inclusion criteria is provided elsewhere.³⁸⁻⁴⁰ Across all cohorts, English or Spanish speaking participants were recruited during pregnancy and were eligible for inclusion if they were at least 18 years of age and not pregnant with multiples. Recruitment for CIOB, IKIDS, and PROTECT began in 2014, 2013, and 2010, respectively, and is ongoing. Recruitment for TIDES occurred between 2010-2012.³⁸⁻⁴⁰ Each cohort was reviewed and approved by the local Institutional Review Board, and all cohort participants provided written informed consent. In the present analysis, we restricted to those with information on oxidative stress and gestational age at delivery and included 1,916 participants (Figure 2), of which 229 were enrolled in CIOB, 221 in IKIDS, 709 in PROTECT, and 757 in TIDES. In CIOB and IKIDS, oxidative stress biomarkers were obtained for all PTBs and a random sample of full-term births. Among the full-term births, we measured oxidative stress among those who had complete covariate data and who were demographically similar to those included in the larger study.³⁸

Oxidative Stress Biomarkers

Urine samples were collected at three time points in PROTECT (mean 18.2, 23.6, and 26.9 weeks gestation), two time points in both CIOB (mean 20.2 and 31.0 weeks gestation) and IKIDS (mean 16.2 and 23.3 weeks gestation), and once in TIDES (mean 32.7 weeks of gestation). Samples were frozen at –80°C prior to analysis of oxidative stress biomarkers. The Eicosanoid Core Laboratory at Vanderbilt University Medical Center quantified the levels of 8-iso-PGF_{2α}, F₂-IsoP-M, and PGF_{2α} using stable isotope dilution gas chromatography-negative ion chemical ionization–mass spectrometry (GC/MS) or liquid chromatography-mass spectrometry (LC/MS).²² Briefly, for the GC/MS analysis, urine was extracted via C-18 Sep-Pak cartridges (Waters Corporation, Milford, MA, USA) prior

to derivatization to the pentafluorobenzyl-ester, as previously described.²² The LC/MS procedure is detailed in supplementary material.

The ratio of 8-iso-PGF_{2α}/PGF_{2α} was used to estimate non-enzymatic vs. enzymatic formation of this biomarker.³⁵ The chemical fraction captures non-enzymatic lipid peroxidation as a result of oxidative stress while the enzymatic fraction is generated from prostaglandin-endoperoxide synthases (or COX) and is reflective of inflammation.³⁵

To account for urinary dilution, oxidative stress biomarkers were corrected for specific gravity (SpG), as previously described.¹⁸ Oxidative stress biomarker concentrations below the limit of detection (LOD; 0.05 ng/mL) were imputed using $LOD / \sqrt{2}$. All SpG-corrected biomarker concentrations were right skewed and natural log transformed for analyses.

Preterm Birth

Gestational age at birth was ascertained through a combination of self-reported date of last menstrual period and first ultrasound estimates in PROTECT,³⁹ best estimated gestational age at delivery from the medical record in CIOB,³⁸ a combination of maternal ultrasound and infant date of birth in IKIDS,³⁸ and from the first available ultrasound or physician's best estimate of gestational age at birth in TIDES.³⁷ PTB subtypes included early preterm (<32 completed weeks gestation), moderate preterm (32 to <34 completed weeks gestation), and late preterm (34 to <37 completed weeks gestation).⁴¹ Births were classified as being of spontaneous origin if the medical record indicated spontaneous labor (CIOB) or if PROM, spontaneous preterm labor, or both were present (PROTECT and TIDES).³⁷⁻³⁹ Mothers self-reported whether the birth was spontaneous in IKIDS.³⁸ PTBs that were medically indicated or of unknown origin were classified as being non-spontaneous.

Statistical Analysis

We examined the distribution of demographic characteristics among the overall study population. The distribution of measured and derived oxidative stress biomarkers was assessed using geometric means, geometric standard deviations (SDs), and selected percentiles. Spearman correlation coefficients were used to examine correlations between oxidative stress biomarkers and gestational age. Generalized additive mixed models with a random intercept for participant ID and a smoothing term for gestational age at sample collection were used to graphically depict levels of oxidative stress biomarkers across gestation.

We calculated geometric mean biomarker concentrations for participants with repeated measurements available. If only one measurement was available for the participant, we used only that measure. For participants with multiple exposure measurements, we calculated intraclass correlation coefficients (ICC) to examine variability in biomarker concentrations across gestation.⁴²

Logistic regression was used to examine the relationship between oxidative stress biomarkers and PTB. Oxidative stress biomarkers were treated as continuous measures, natural log transformed, and standardized to the population's interquartile range (IQR), which corresponds to an increase from the 25th to 75th percentile, equating to an increase

of 1.03, 0.71, and 2.1 ng/mL for 8-iso-PGF_{2α}, F₂-IsoP-M, and PGF_{2α}, respectively. This was done for consistency with prior studies and to increase interpretability,²⁶⁻²⁷⁻³⁷ as we felt that an IQR increase repeated a more meaningful change as opposed to a one ng/mL increase. We additionally examined spontaneous PTB, non-spontaneous PTB, and PTB categories (early/moderate vs. late) as separate outcomes. Early and moderate PTBs were combined due to the small number of early PTBs (N=19 early PTBs). Covariates included an indicator for cohort, average gestational weeks at sample collection, maternal age, maternal educational attainment, marital status, and pre-pregnancy body mass index (BMI). These confounders were chosen based on their known associations with oxidative stress and PTB in the literature and in our study population.¹⁶⁻⁴³⁻⁴⁴

We conducted several sensitivity analyses. To assess non-linear relationships, we examined quartiles of oxidative stress in relation to all PTB outcomes. We also assessed the relationship between oxidative stress biomarkers and continuous gestational age using linear regression. We additionally examined the relationship between oxidative stress and all PTBs stratified by infant sex, as prior work suggests that antioxidant status and oxidative stress levels may differ by fetal sex.⁴⁵⁻⁴⁶ Given that our study design involved heterogeneous birth cohorts, we applied four complementary approaches to determine whether any of our results could be attributable to underlying differences in individual cohorts. First, we examined adjusted associations between oxidative stress biomarkers and all PTBs stratified by cohort. Second, we conducted a meta-analysis of the individual cohort-specific estimates to compare with the combined sample analysis.⁴⁷⁻⁴⁸ Third, to determine if associations were driven by specific cohorts, we included an interaction term for cohort*oxidative stress biomarkers in the models that included all PTBs as an outcome. Finally, to address the influence of cohort heterogeneity on our results, we conducted a leave-one-out analysis removing one cohort at a time.

RESULTS

Most participants in our analytic sample had normal pre-pregnancy BMI (52%) and self-identified as White (40%) or Latina (44%) (Table 1). IKIDS had the highest percentage of White participants (81%) while PROTECT had the highest percentage of Latinas (100%) (Table 1). In the overall sample, 11% of births were preterm and 6% of births were spontaneous preterm. Mothers who delivered preterm compared with term were more likely to have completed some college or less and be unmarried (Supplemental Table 1).

The geometric mean biomarker concentration was highest for PGF_{2α} (geometric mean=2.19 ng/mL [geometric SD=2.15]), followed by 8-iso-PGF_{2α} (geometric mean=1.19 ng/mL [geometric SD=1.95]) and F₂-IsoP-M (geometric mean=0.81 ng/mL [geometric SD=2.69]) (Supplemental Table 2). The concentration of F₂-IsoP-M was highest among CIOB participants (1.80 ng/mL), whereas the concentrations of 8-iso-PGF_{2α} and PGF_{2α} were highest among PROTECT participants (1.81 ng/mL and 2.78 ng/mL, respectively) (Supplemental Table 2). The ICC value for 8-iso-PGF_{2α} was 0.54 (95% confidence interval [CI]=0.50, 0.58). ICC values for F₂-IsoP-M and PGF_{2α} indicated greater variability (ICC=0.23, 95% CI=0.17, 0.29 and ICC=0.11, 95% CI= 0.05, 0.17, respectively). When visually examining the levels of 8-iso-PGF_{2α} and PGF_{2α} across gestation, we observed

slight decreases towards the end of pregnancy. Compared with those who delivered full term, the levels of F₂-IsoP-M in those with PTBs were elevated beginning in mid-pregnancy (Figure 3). Gestational age at delivery was negatively correlated with all oxidative stress biomarkers (Supplemental Figure 1). The strongest correlation observed between measured oxidative stress biomarkers was between 8-iso-PGF_{2α} and PGF_{2α} (Spearman ρ=0.59).

IQR increases in 8-iso-PGF_{2α} and F₂-IsoP-M were associated with higher odds of all PTBs after adjustment for confounders (odds ratio [OR]=1.19, 95% CI=0.94, 1.50; OR=1.29, 95% CI 0=1.11, 1.51, respectively) (Table 2). When spontaneous PTB was the outcome, the effect of F₂-IsoP-M was greater in magnitude (OR=1.47, 95% CI 0=1.16, 1.90). When examining categories of PTB, an IQR increase in any of the biomarkers was associated with higher odds of early or moderately preterm delivery, with PGF_{2α} and the enzymatic fraction, which reflect inflammatory pathways, being the greatest in magnitude (Table 2). Additional adjustment for smoking status or alcohol consumption did not meaningfully change effect estimates.

When continuous gestational age at delivery was the outcome, an IQR increase in 8-iso-PGF_{2α} and F₂-IsoP-M was associated with shorter gestational age (Supplemental Table 3). When stratifying by infant sex, the association between 8-iso-PGF_{2α} and all PTBs persisted only among females, although CIs were wide (Supplemental Table 4). When examining quartiles of oxidative stress biomarkers in relation to all and spontaneous PTBs, associations were generally greater in magnitude when comparing the upper quartile to the lowest quartile, suggesting evidence of a dose response (Supplemental Table 5).

In our sensitivity analysis allowing for interaction between cohort and oxidative stress, we observed no evidence of interaction (Supplemental Table 6). In analyses stratified by cohort, the relationship between 8-iso-PGF_{2α} and all PTBs was strongest for the PROTECT cohort (OR=1.57, 95% CI 0=0.95, 2.61), whereas the relationship between all PTBs and F₂-IsoP-M was strongest for the TIDES cohort (OR=1.65, 95% CI= 0.99, 2.71) (Supplemental Table 7).²⁶⁻³⁷ Results from our meta-analysis were similar to the pooled combined cohort analysis (Table 2). The OR estimates were similar in the leave-one-out analysis, although CIs were less precise (Supplemental Table 8).

COMMENT

Principal Findings

Our pooled cohort study examined the association between oxidative stress and PTB. We observed that F₂-IsoP-M concentrations, averaged across pregnancy, were positively associated with odds of PTB. The association was greater in magnitude for PTB of spontaneous origin. 8-iso-PGF_{2α}, the parent compound, was similarly associated with modestly higher odds of delivering preterm, particularly delivering prior to 34 weeks of completed gestation. A growing body of evidence links 8-iso-PGF_{2α} to socioeconomic disadvantage, environmental chemical exposures, and psychosocial stress.^{1-14-16,18,30,49,50} Our findings support the hypothesis that oxidative stress is one pathway by which chemical and non-chemical exposures may lead to PTB.^{15,51-53}

Results in the Context of What is Known

In preliminary analyses within a subset of the PROTECT cohort, as well as within the TIDES cohort, we observed that higher concentrations of 8-iso-PGF_{2α} and F₂-IsoP-M were associated with higher odds of all and spontaneous PTBs.²⁶⁻³⁷ The present study confirms these findings with a much larger sample size. Our findings are also supported by studies conducted in other research groups. A Chicago-based study of 237 preterm infants without congenital anomalies found that cord blood levels of 8-iso-PGF_{2α} were elevated among those who delivered prior to 28 weeks completed gestation relative to those who were born between 34 and 36 weeks.⁵⁴ This suggests that 8-iso-PGF_{2α} may cross the placenta, which is supported by our finding that levels of 8-iso-PGF_{2α} decreased slightly across gestation. Additionally, a study conducted among infants suspected of having patent ductus arteriosus found that plasma 8-iso-PGF_{2α} levels measured 24-48 hours post-birth were higher among infants born prior to 32 weeks gestation relative to those born at term.⁵⁵ In prior work in LIFECODES, a predominately white and high socioeconomic status birth cohort in Boston, higher concentrations of urinary 8-iso-PGF_{2α}, averaged across the first and second trimesters, were associated with higher odds of all PTBs and spontaneous PTB.²⁷ In that study, ORs were greater in magnitude when 8-iso-PGF_{2α} was measured at median 18 and 26 weeks, relative to 10 weeks.²⁷ OR estimates for averaged oxidative stress were also larger in that study than what we observed (for all PTBs, OR=2.22 [95% CI 0=1.47, 3.36] vs. OR=1.19 [95% CI 0=0.94, 1.5]).²⁷ Differences may be due to statistical power, as the CIs in our study were more precise and we had a larger number of cases (126 versus 208 cases of PTBs).²⁷ While the effect size in our study was smaller, our findings indicate that the positive association between elevated oxidative stress and PTB persists across racial, ethnic, and socioeconomic groups. Other studies have also suggested that oxidative stress biomarkers are associated with a higher risk of PTB or shorter gestational duration.^{2,56-58}

A novel aspect of our study is that we used a ratio formula of 8-iso-PGF_{2α} to PGF_{2α} to determine the amount of 8-iso-PGF_{2α} derived from oxidative stress and inflammation pathways (i.e., the chemical and enzymatic fractions, respectively).³⁵ This represents an advancement over prior studies that have interpreted 8-iso-PGF_{2α} solely as an indicator of oxidative stress. We observed that elevated levels of the enzymatic fraction were associated with higher odds of early or moderate PTB and lower odds of non-spontaneous PTB. This may suggest differential mechanisms linking oxidative stress and inflammation to PTB subtypes, including early versus late preterm delivery.

Clinical Implications

We observed that an IQR increase in 8-iso-PGF_{2α} and F₂-IsoP-M were associated with a 17% and 47% increase in odds of spontaneous PTB, respectively. These estimates are similar in magnitude to what has been observed for other known risk factors for spontaneous PTB, including infection (OR=1.23, 95% CI= 0.96, 1.57)⁵⁹ and prior preterm delivery (absolute risk= 25%, 95% CI= 24%, 26%).⁶⁰ In addition to acting as a precursor to spontaneous labor,¹ oxidative stress also leads to apoptosis, DNA damage, and shortened telomere length, potentially leading to PROM.⁵⁶⁻⁶¹ Elevated oxidative stress can also increase the risk of infection and placental dysfunction.⁵⁶ Early indicators of PTB, such as intrauterine infection, may lead to the production of pro-inflammatory cytokines and

ultimately the release of free radicals, inducing oxidative stress.⁶² $\text{PGF}_{2\alpha}$, which is more reflective of underlying inflammatory processes, may also lead to PTB through increased cytokine production, as $\text{PGF}_{2\alpha}$ is stimulated in response to proinflammatory cytokines, which promote cervical ripening and stimulate uterine contractions.^{1,33,34,63}

While the goal of our study was to examine associations between continuous measures of oxidative stress biomarkers and PTB, an important next step of this work is to determine cut points for high and low oxidative stress, which would allow us to evaluate the diagnostic performance of these biomarkers. Prior work assessing the prediction of eicosanoids and oxidative stress biomarkers within the LIFECODES cohort that found many lipid biomarkers (53 eicosanoids) were needed to have modest prediction accuracy (area under the receiver operating curve (AUC) > 0.7).⁶⁴ In comparison, AUC values for individual oxidative stress biomarkers were low (AUC = 0.52 for 8-OH-dG and AUC = 0.64 for protein oxidation markers).⁶⁴ In light of this prior work,⁶⁴ and the limited number of oxidative stress biomarkers used in our analysis, the implications of our results for clinical and upstream diagnostic applications remain uncertain. Therefore, future analyses of a broader scope of oxidative stress biomarkers should assess how their combined diagnostic performance varies across trimesters, which may enable clinicians to identify high risk individuals early in pregnancy and allocate them to potential treatments, such as supplemental progesterone.⁶⁵

Strengths and Limitations

An important strength of our study is that we leveraged four prospective cohorts, increasing the generalizability of our findings. Our sample was composed of nearly 2,000 births (including 60% non-White) spanning a wide array of socioeconomic strata. We were also able to examine different categories of PTB and assess spontaneous and non-spontaneous PTB as separate outcomes. This is particularly important, as we observed the strongest effects for spontaneous and early or moderate PTB. Additionally, F_2 -IsoPs are considered to be the “gold standard” biomarkers of oxidative stress, as they indicate endogenous lipid peroxidation, are not confounded by dietary lipid intake, and measurement does not require fasting.⁶⁶⁻⁶⁷ On a population level, 8-iso- $\text{PGF}_{2\alpha}$ levels in a spot urine sample are similar to what is observed with a 24-hour fasting sample.⁶⁸ Finally, in addition to 8-iso- $\text{PGF}_{2\alpha}$, we examined two other biomarkers of oxidative stress and inflammation, F_2 -IsoP-M and $\text{PGF}_{2\alpha}$, which we observed to be strongly associated with spontaneous and early or moderate PTB, respectively.

We also acknowledge this study’s limitations. First, for participants with repeated biomarker measurements, the geometric mean biomarker concentration was used as our primary independent variable. While this does allow us to create a more stable estimate of oxidative stress across pregnancy, it limits our ability to look at windows of susceptibility. Additionally, our results may be subject to selection bias, as those who delivered preterm were missing an oxidative stress measurement at later study visits. However, any bias is likely to be minimal and would likely drive results toward the null value, as only those who delivered early preterm (N=19) could possibly have missed subsequent study visits. For those participants who delivered moderate and late preterm, none were missing oxidative stress measurements. While our study population spanned a wide array geographic

groups, our analytic sample included few participants who were not college-educated and a small proportion of African Americans, which may limit generalizability to these groups. Additionally, assessment of spontaneous PTB varied across cohorts, which may have resulted in outcome misclassification. Lastly, information on prior PTB, cervical insufficiency, and use of supplemental progesterone was unavailable in our study population. Thus, we were unable to assess their associations with oxidative stress biomarkers and PTB.

Research Implications and Conclusions

We observed that elevated oxidative stress biomarkers were positively associated with PTB. Particularly, we found levels of F₂-IsoP-M to be higher among those who delivered spontaneously preterm. PGF_{2α}, which is more reflective of underlying inflammatory processes, was most strongly associated with early and moderate PTB, suggesting that the underlying mechanisms linking oxidative stress and inflammation to PTB differ by preterm clinical subtype. While randomized trials assessing the impact of antioxidant supplementation and subsequent birth outcomes have produced negative results,⁶⁹⁻⁷⁰ it is possible that antioxidant supplementation is non-specific in the sense that it might not affect F₂-IsoPS. Importantly, upstream systems level changes (e.g. increased access to healthy foods and to safe and walkable neighborhoods) may also reduce the burden of stressors and promote healthy behaviors, such as achieving a healthy weight prior to and during pregnancy, undertaking physical activity, and limiting alcohol consumption, which in turn may reduce chronic inflammation and oxidative stress^{7,18-43-71} Future research should focus on examining oxidative stress as a mediating pathway linking environmental chemical and social stressor exposures to PTB and identifying modifiable risk factors for elevated oxidative stress, which could inform clinical practice, including the early identification of at-risk pregnancies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

The datasets for this manuscript are not publicly available because, per the NIH-approved ECHO Data Sharing Policy, ECHO-wide data have not yet been made available to the public for review/analysis. Requests to access the datasets should be directed to the ECHO Data Analysis Center, ECHO-DAC@rti.org.

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AJOG at a Glance

- **A.** Elevated oxidative stress has been associated with preterm birth. However, prior studies have been limited by small sample size and were conducted in primarily White populations, which does not reflect the diversity in the United States.
- **B.** Oxidative stress, as measured by 8-iso-prostaglandin- $F_{2\alpha}$, 2,3-dinor-5,6-dihydro-8-iso-prostaglandin- $F_{2\alpha}$, and prostaglandin $F_{2\alpha}$ in urine, is associated with increased odds of preterm birth, particularly preterm birth of spontaneous origin and delivery prior to 34 completed weeks of gestation.
- **C.** Among a racially, ethnically, and demographically diverse study population spanning the mainland United States and Puerto Rico, our study supports prior findings that elevated oxidative stress is on the causal pathway to preterm birth. Results from our study indicate that underlying mechanisms linking oxidative stress to preterm birth differ by preterm clinical subtype.

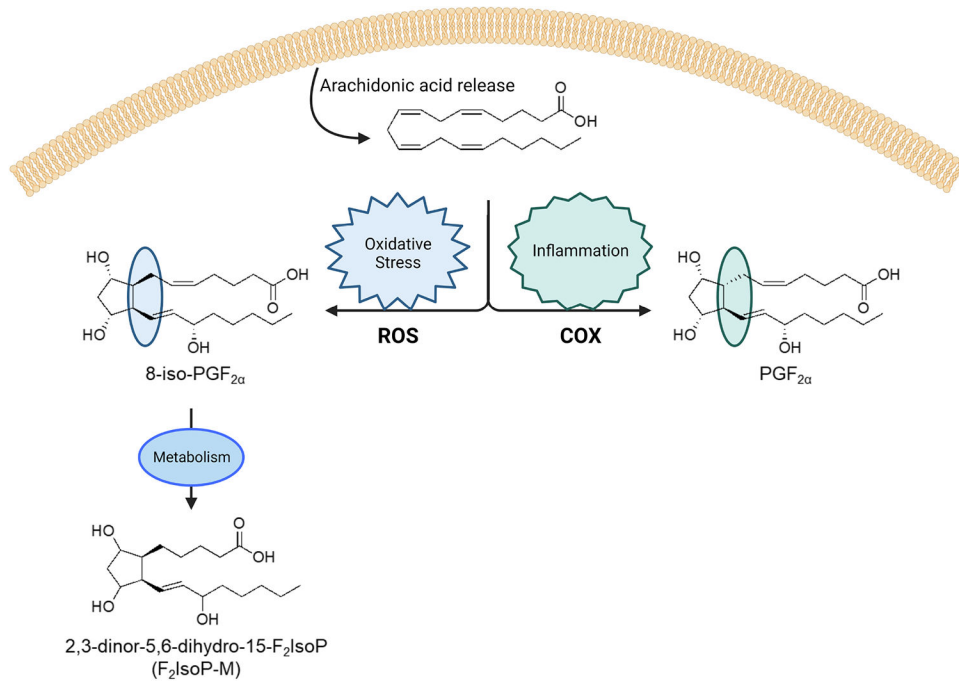


Figure 1. Biosynthetic pathways showing how oxidative stress biomarkers measured in the present study (8-iso-PGF_{2α}, F₂-IsoP-M, PGF_{2α}) are generated.

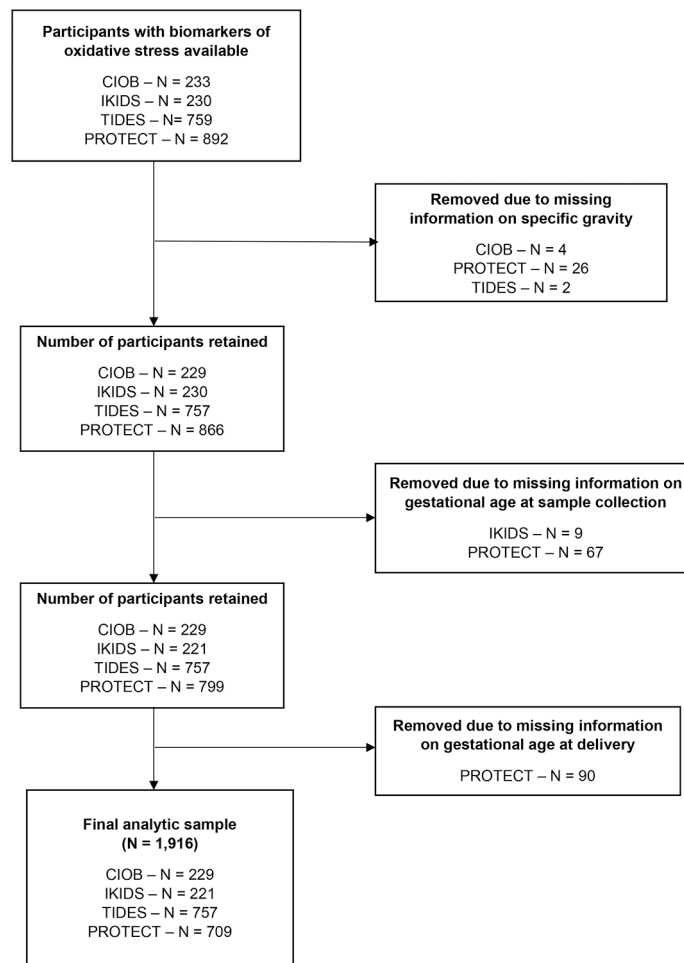


Figure 2. Flowchart indicating participant selection into final analytic sample. CIOB, Chemicals in Our Bodies; IKIDS, Illinois Kids Development Study; PROTECT, Puerto Rico Testsite for Exploring Contamination Threats; TIDES, The Infant Development and Environment Study.

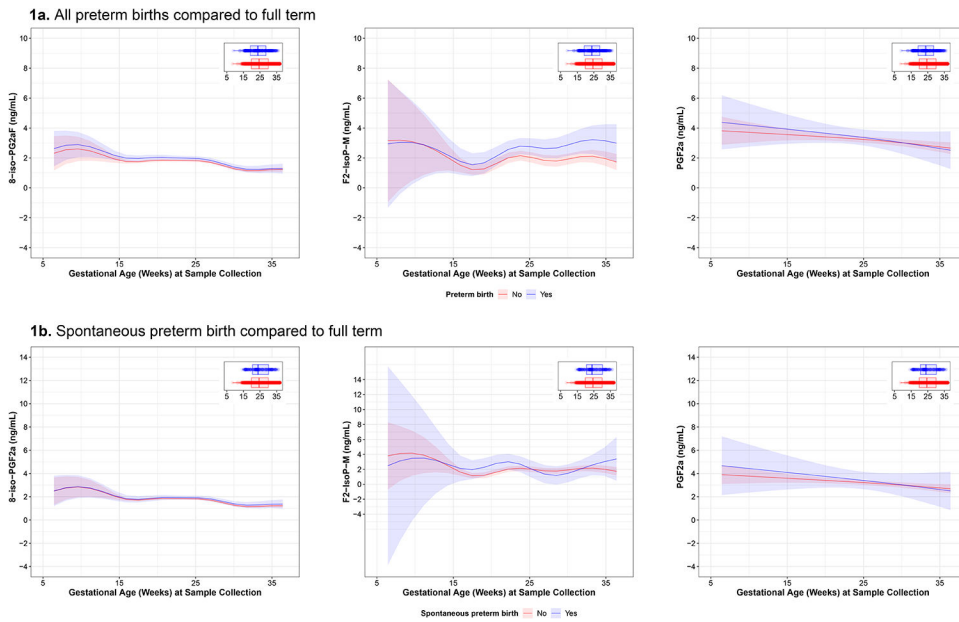


Figure 3.

Predicted values (95% confidence intervals) of specific gravity-corrected urinary oxidative stress biomarker concentrations by gestational age at sample collection in all preterm, spontaneous preterm only, and full-term births obtained from generalized additive mixed models with a random intercept for participant ID.

Table 1.

Distribution of demographic characteristics and pregnancy outcomes in the overall study population and stratified by individual cohort.

	Overall (N=1,916)	CIOB (N=229)	IKIDS (N=221)	PROTECT (N=709)	TIDES (N=757)
	N (%)	N (%)	N (%)	N (%)	N (%)
Preterm birth					
No	1708 (89%)	189 (83%)	196 (89%)	627 (88%)	696 (92%)
Yes	208 (11%)	40 (17%)	25 (11%)	82 (12%)	61 (8%)
Maternal age (years)					
18-24	405 (21%)	23 (10%)	14 (6%)	269 (37%)	99 (13%)
25-29	476 (25%)	26 (11%)	73 (33%)	220 (31%)	157 (21%)
30-34	580 (30%)	86 (38%)	105 (48%)	142 (21%)	247 (33%)
35	412 (22%)	94 (41%)	29 (13%)	78 (11%)	211 (28%)
Missing	43 (2.2%)	0 (0%)	0 (0%)	0 (0%)	43 (5.7%)
Pre-pregnancy BMI (kg/m²)					
Underweight	75 (4%)	6 (3%)	6 (3%)	47 (7%)	16 (2%)
Normal	991 (52%)	116 (51%)	120 (54%)	331 (47%)	424 (56%)
Overweight	436 (23%)	59 (26%)	43 (19%)	174 (25%)	160 (21%)
Obese	360 (19%)	39 (17%)	48 (22%)	125 (18%)	148 (20%)
Missing	54 (2.8%)	9 (3.9%)	4 (1.8%)	32 (4.5%)	9 (1.2%)
Maternal race/ethnicity					
White	772 (40%)	102 (45%)	179 (81%)	<5	490 (65%)
Black	114 (6%)	13 (6%)	11 (5%)	<5	90 (12%)
Asian/Pacific Islander	108 (6%)	36 (16%)	14 (6%)	<5	58 (8%)
Latina	849 (44%)	70 (31%)	4 (2%)	707 (100%)	68 (9%)
Other/Multi-Racial	49 (3%)	8 (3%)	13 (6%)	<5	28 (4%)
Missing	24 (1.3%)	0 (0%)	0 (0%)	0 (0%)	23 (3.0%)
Maternal education					
<High school	126 (7%)	24 (10%)	<5	42 (6%)	59 (8%)
High school or some college	417 (22%)	55 (24%)	30 (14%)	193 (27%)	139 (18%)
College degree	752 (39%)	55 (24%)	81 (37%)	381 (54%)	235 (31%)
Graduate	610 (32%)	93 (41%)	109 (49%)	90 (13%)	318 (42%)
Missing	11 (0.6%)	2 (0.9%)	0 (0%)	3 (0.4%)	6 (0.8%)
Marital status					
Married	1266 (66%)	167 (73%)	201 (91%)	371 (52%)	527 (70%)
Living together	351 (18%)	40 (17%)	10 (5%)	198 (28%)	103 (14%)
Single	292 (15%)	20 (9%)	10 (5%)	137 (19%)	125 (17%)
Missing	7 (0.4%)	2 (0.9%)	0 (0%)	3 (0.4%)	2 (0.3%)
Parity					
0	862 (45%)	126 (55%)	85 (38%)	261 (37%)	390 (52%)
1+	896 (47%)	98 (43%)	136 (62%)	342 (48%)	320 (42%)

	Overall (N=1,916)	CIOB (N=229)	IKIDS (N=221)	PROTECT (N=709)	TIDES (N=757)
	N (%)	N (%)	N (%)	N (%)	N (%)
Missing	158 (8.2%)	5 (2.2%)	0 (0%)	106 (15.0%)	47 (6.2%)
Current smoker					
No	1772 (92%)	227 (99%)	217 (98%)	694 (98%)	634 (84%)
Yes	73 (4%)	0 (0%)	<5	13 (2%)	56 (7%)
Missing	71 (3.7%)	2 (0.9%)	0 (0%)	2 (0.3%)	67 (8.9%)

Preterm birth includes all births occurring prior to 37 weeks of gestation. Non-spontaneous preterm b includes all preterm births that were of non-spontaneous origin (medically indicated or unknown). Early/moderate preterm birth includes birth occurring prior to 34 completed weeks of gestation. Late preterm birth includes births occurring between 34 and 36 completed weeks of gestation. BMI, body mass index. CIOB, Chemicals in Our Bodies; IKIDS, Illinois Kids Development Study; LOD, limit of detection; PROTECT, Puerto Rico Testsite for Exploring Contamination Threats; SD, standard deviation; TIDES, The Infant Development and Environment Study.

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Table 2.

Odds ratios (95% confidence intervals) for preterm birth, spontaneous preterm birth, non-spontaneous preterm birth, and preterm birth subtypes in association with an interquartile range increase in averaged concentrations of urinary specific gravity–corrected oxidative stress biomarkers (ng/mL) within the overall sample and in a meta-analysis of cohort-specific estimates.

	Unadjusted			Adjusted			Meta-analysis	
	N (PTB, FTB)	OR	(95% CI)	N (PTB, FTB)	OR	(95% CI)	OR	(95% CI)
All preterm births								
Measured								
8-iso-PGF _{2α}	(208, 1708)	1.32	(1.07, 1.64)	(190, 1623)	1.19	(0.94, 1.5)	1.16	(0.92, 1.40)
F ₂ -IsoP-M	(208, 1708)	1.25	(1.10, 1.44)	(190, 1623)	1.29	(1.11, 1.51)	1.22	(1.07, 1.37)
PGF _{2α}	(208, 1708)	1.13	(0.95, 1.35)	(190, 1623)	1.04	(0.86, 1.25)	1.06	(0.88, 1.25)
Derived								
8-iso-PGF _{2α} chemical	(208, 1708)	1.22	(0.98, 1.51)	(190, 1623)	1.11	(0.88, 1.41)	1.08	(0.84, 1.32)
8-iso-PGF _{2α} enzymatic	(208, 1708)	1.02	(0.86, 1.20)	(190, 1623)	0.98	(0.83, 1.16)	1.00	(0.82, 1.18)
Spontaneous preterm birth								
Measured								
8-iso-PGF _{2α}	(112, 1708)	1.21	(0.91, 1.61)	(99, 1623)	1.17	(0.86, 1.61)	1.13	(0.80, 1.45)
F ₂ -IsoP-M	(112, 1708)	1.24	(1.03, 1.51)	(99, 1623)	1.47	(1.16, 1.90)	1.38	(1.14, 1.63)
PGF _{2α}	(112, 1708)	1.19	(0.94, 1.51)	(99, 1623)	1.13	(0.88, 1.45)	1.12	(0.86, 1.38)
Derived								
8-iso-PGF _{2α} chemical	(112, 1708)	1.04	(0.79, 1.38)	(99, 1623)	1.02	(0.75, 1.40)	0.98	(0.67, 1.29)
8-iso-PGF _{2α} enzymatic	(112, 1708)	1.14	(0.91, 1.46)	(99, 1623)	1.13	(0.89, 1.46)	1.13	(0.88, 1.39)
Non-spontaneous preterm birth								
Measured								
8-iso-PGF _{2α}	(96, 1708)	1.48	(1.09, 1.99)	(91, 1623)	1.22	(0.88, 1.69)	1.19	(0.86, 1.52)
F ₂ -IsoP-M	(96, 1708)	1.27	(1.06, 1.53)	(91, 1623)	1.18	(0.98, 1.42)	1.10	(0.91, 1.29)
PGF _{2α}	(96, 1708)	1.08	(0.85, 1.39)	(91, 1623)	0.96	(0.74, 1.25)	1.01	(0.74, 1.27)
Derived								
8-iso-PGF _{2α} chemical	(96, 1708)	1.49	(1.09, 2.05)	(91, 1623)	1.24	(0.89, 1.74)	1.20	(0.85, 1.55)
8-iso-PGF _{2α} enzymatic	(96, 1708)	0.90	(0.72, 1.14)	(91, 1623)	0.85	(0.68, 1.07)	0.87	(0.63, 1.11)
Early/Moderate preterm								
Measured								
8-iso-PGF _{2α}	(42, 1708)	1.61	(1.06, 2.44)	(34, 1623)	1.36	(0.81, 2.28)	1.22	(0.72, 1.72)
F ₂ -IsoP-M	(42, 1708)	1.17	(0.95, 1.48)	(34, 1623)	1.37	(1.03, 1.9)	1.21	(0.91, 1.51)
PGF _{2α}	(42, 1708)	1.83	(1.25, 2.68)	(34, 1623)	1.48	(0.96, 2.31)	1.60	(1.16, 2.05)
Derived								
8-iso-PGF _{2α} chemical	(42, 1708)	1.33	(0.86, 2.07)	(34, 1623)	1.19	(0.71, 2.03)	0.98	(0.47, 1.49)
8-iso-PGF _{2α} enzymatic	(42, 1708)	1.83	(1.17, 3.09)	(34, 1623)	1.47	(0.94, 2.49)	1.65	(1.13, 2.17)

	Unadjusted			Adjusted			Meta-analysis	
	N (PTB, FTB)	OR	(95% CI)	N (PTB, FTB)	OR	(95% CI)	OR	(95% CI)
Late preterm birth								
Measured								
8-iso-PGF _{2α}	(165, 1708)	1.25	(0.98, 1.59)	(155, 1623)	1.16	(0.89, 1.5)	1.13	(0.86, 1.39)
F ₂ -IsoP-M	(165, 1708)	1.31	(1.11, 1.55)	(155, 1623)	1.26	(1.07, 1.51)	1.21	(1.03, 1.39)
PGF _{2α}	(165, 1708)	1.01	(0.83, 1.22)	(155, 1623)	0.97	(0.79, 1.19)	0.97	(0.76, 1.18)
Derived								
8-iso-PGF _{2α} chemical	(165, 1708)	1.18	(0.93, 1.51)	(155, 1623)	1.09	(0.85, 1.42)	1.08	(0.81, 1.34)
8-iso-PGF _{2α} enzymatic	(165, 1708)	0.91	(0.77, 1.09)	(155, 1623)	0.91	(0.76, 1.1)	0.92	(0.73, 1.11)

Note: Unadjusted models are minimally adjusted for cohort and averaged gestational age (weeks) at sample collection. Adjusted models include maternal age, education, marital status, pre-pregnancy body mass index, averaged gestational age (weeks) at sample collection, and cohort. Early/moderate preterm birth models were not adjusted for smoking status due to a small number of smokers in this group. Preterm birth includes all births occurring prior to 37 weeks of gestation. Non-spontaneous preterm birth includes all preterm births that were of non-spontaneous origin (medically indicated or unknown). Early/moderate preterm birth includes birth occurring prior to 34 completed weeks of gestation. Late preterm birth includes births occurring between 34 and 36 completed weeks of gestation. CI, confidence interval; FTB, full-term birth; OR, odds ratio; PTB, preterm birth.