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Oxidative stress and fetal weight: observational findings from a pregnancy cohort in New York City

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OBJECTIVE: To examine associations between oxidative stress and fetal weight across pregnancy.
STUDY DESIGN: Cohort study of pregnant participants from 2016-2021 in New York City with urinary lipid, protein, and DNA oxidative stress biomarkers (<18, 18–25, >25 weeks) and estimated fetal weight from ultrasound fetal biometry with the HadlockIII formula (20, 30, 36 weeks).
RESULT: Among 1408 participants, oxidative stress biomarkers of lipid peroxidation and DNA damage were associated with smaller estimated fetal weight at 30 and 36 weeks (ranging from B = −3.9 grams/unit increase [95% CI: −6.9, −0.9; *8,15 − PGF2α*] to −20.3 [95% CI: −27.9, −12.8; *8 − OHdG*]), particularly among fetuses at the 25th percentile. Oxidative stress biomarkers of protein damage were associated with larger estimated fetal weight at 20 (3.4 [95% CI: 1.2, 5.7]) and 36 weeks (16.5 [95% CI: 5.2, 27.8]).
CONCLUSION: These findings advance our understanding of different oxidative stress pathways and their potential role in fetal growth.

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INTRODUCTION

Adequate fetal weight predicts healthy birthweight, a key indicator of health given its associations with long-term outcomes, morbidity, and mortality [1]. Thus, estimating fetal weight with ultrasound is common during routine obstetric care to better predict and manage maternal and perinatal morbidity and mortality [2]. Adequate fetal growth and appropriate development relies on placental nutrient exchange. As a result, fetal weight is likely sensitive to environmental risk factors and psychosocial stress that elevate blood pressure, which can constrict blood flow to the placenta [3] and raise oxidative stress [4, 5]. Oxidative stress levels increase when concentrations of harmful free radicals surpass the balance of protective antioxidants, leading to chronic inflammation [6]. Scientists have suspected oxidative stress to be an indicator of pregnancy complications related to fetal weight [7, 8]. Yet, studies often use birthweight as a proxy of fetal growth [1, 2]. Understanding associations between oxidative stress and direct estimates of fetal weight in a community-based cohort would advance our understanding of fetal weight trajectories and developmental programming.

Researchers have accumulated findings from animal, cellular, and infectious disease models that suggest a relation between inflammatory oxidative stress pathways and fetal weight in the setting of adverse infant health outcomes [7, 8]. For example, excess oxidative stress near the end of the fetal period has been associated with shorter gestational length and smaller birthweight outcomes [7, 9]. Studies in smaller samples of 30-50 pregnant participants [10–12] have demonstrated associations between individual measures of oxidative stress and fetal growth restriction but a relation with fetal weight was not identified within a preterm birth cohort of 482 participants [13]. Oxidative stress has also been closely linked to preterm birth [14], which has been tied to fetal growth restriction. Understanding whether higher oxidative stress is associated with fetal size across gestation even when clinically evident medical conditions are not present (e.g., fetal growth restriction, premature birth) can inform our knowledge of the physiological mechanisms linking pregnancy exposures with consequential birth outcomes.

The prenatal period is a significant life stage when developing tissues and vasculature may be extra sensitive to oxidative stress signaling during fetal stages of rapid growth and development [15]. Emerging studies have measured oxidative stress at multiple timepoints to assess their associations with pregnancy outcomes [8, 14, 16]. The study aimed to assess relations between seven oxidative stress biomarkers (OSB) of lipid, protein, and DNA damage at three time points in pregnancy and estimated fetal weight (EFW) predicted through clinically obtained ultrasounds in a community-based sample with racial, ethnic, and socioeconomic diversity. Investigation of OSBs produced across lipid, protein, and DNA molecules offers a more granular insight of underlying molecular mechanisms, increasing our insight into pathways linking chronic inflammation to fetal weight. We hypothesized

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that higher levels of OSBs measured in pregnancy would be associated with smaller EFW, particularly among fetuses with smaller EFW, and that this would vary by type of OSB (e.g., protein v. lipid). We also tested windows of heighted susceptibility for any association of OSB and EFW, without an a priori hypothesis because of sparsity of data on repeated OSB measures during gestation.

METHODS

Study sample

Our sample is from a population-based, prospective birth cohort (additional details available elsewhere [17]). In brief, we enrolled pregnant participants from three hospitals in New York City between March 2016 and November 2021. Participants eligible to enter the study were 18 years or older, less than 18 weeks pregnant at enrollment, and fluent in English, Spanish, or Chinese. Enrolled participants responded to questionnaires and provided urine samples during prenatal study visits at <18 weeks, 18–25 weeks, and >25 weeks. The sample size was based on the full cohort of participants that met inclusion criteria; the final sample size was similar to or larger than comparable studies in this area [8, 13, 16, 18]. Of the 3011 participants with singleton fetal ultrasound data, urinary OSBs were measured in a subset of $n = 1408$ (46.8%). These 1408 pregnant participants had comparable sociodemographic characteristics to the 3011 participants, including maternal age, education level, racial distribution, and marital status. This study was approved by the Institutional Review Board at NYU Grossman School of Medicine in accordance with ethical codes and applicable federal regulations and all participants provided written informed consent. This study followed STROBE reporting guidelines.

Estimated fetal weight

Since clinically obtained ultrasounds were performed at varying gestational ages, we predicted EFW using an approach previously published by our team [19, 20], enabling meaningful comparisons. We extracted fetal biometry measures from ultrasounds conducted as part of clinical prenatal care from electronic health records. Licensed sonographers conducted ultrasounds and recorded measurements in millimeters on fetal biparietal diameter, head circumference, abdominal circumference, and femur length. After cleaning the dataset to remove biologically improbable values, we used Hadlock's three parameter (Hadlock-III) formula, which incorporates abdominal circumference, head circumference, and femur length, to estimate fetal weight [21]. We relied on guidelines set forth by the American College of Obstetricians and Gynecologists [22] to determine gestational age. Specifically, dating was based on the last menstrual period if available and updated based on ultrasound dating (~6%) if the gestational age exceeded 5 days from an ultrasound prior to 9 + 0 weeks gestation, or more than 7 days from an ultrasound between 9 and 14 + 0 weeks gestation.

To address variability in ultrasound timing, we predicted EFW at 20, 30, and 36 weeks gestation for all singleton live births. As described elsewhere [20], we applied linear mixed-effects modeling with individual random effects based on the gestational age B-spline basis matrix for fetal biometry prediction [23]. The B-spline basis is a mathematical tool that captures intricate potential non-linear relationships between gestational age and each growth parameter. We conservatively selected two knots to shape the B-spline curve, specifically chosen as quantiles, with values of 20 and 27 to coincide with the anatomy scan and the transition between the second and third trimester, respectively. As shown in Supplementary Fig. 1, the predicted values closely align with observed data, indicating both high accuracy and model fit.

The American College of Obstetrics and Gynecology recommends at least one mid-pregnancy ultrasound between 18 and 22 weeks of gestation [24]. Ultrasounds obtained outside this mid-pregnancy scan may not be representative of the general pregnant population, as they may have been conducted for patients with additional need for fetal monitoring. In our sample, 84.6% of participants had scans beyond 22 weeks and 76.0% had scans beyond 30 weeks. While we did not have the clinical indications of each ultrasound, rates of adverse pregnancy outcomes in our sample was comparable to the general population [25, 26], so the additional scans may also reflect the frequent imaging practices of an academic center.

Oxidative stress biomarkers

We measured seven OSBs in urine samples collected at up to three separate time points from each participant. The study used urine samples because they have found to be are non-inferior to serum samples [27], are used in comparable studies [18, 28], and enhance feasibility for large cohort research [29]. Mean (±SD) gestational ages were 10.8 (± 3.4) for early pregnancy, 20.8 (± 2.2) for mid-pregnancy, and 29.3 (± 3.6) for late pregnancy visits. Urine samples were collected in polypropylene containers and stored at -80°C for a maximum of 1–2 years until measurements were performed at the Wadsworth Center, New York State Department of Health. OSBs in urine are stable for up to several years, particularly when stored at this temperature [30, 31]. We used high performance liquid chromatography interfaced with tandem mass spectrometry to measure seven OSBs of lipid, DNA, and protein damage. Lipid biomarkers included four bioactive forms of *F_2-isoprostanes*—prostaglandin-like compounds generated from peroxidation of arachidonic acid—including *8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$), 11β-prostaglandin $F_{2\alpha}$ (11-$PGF_{2\alpha}$), 15(R)-prostaglandin $F_{2\alpha}$ (15-$PGF_{2\alpha}$), 8-iso-15(R)-prostaglandin $F_{2\alpha}$ (8,15-$PGF_{2\alpha}$)*, and *Malondialdehyde (MDA)* –produced from peroxidation of polyunsaturated fatty acids in cells. Other OSBs measured included *o,o′−dityrosine (diY)*, a protein biomarker that is a product of radical oxidation of tyrosine, and *8−hydroxy − 2′−deoxyguanosine[8 − OHdG]*, a biomarker of nucleic acid oxidation. In our analytic sample, 8.6% were missing urine samples at the first timepoint, 28.9% the second timepoint, and 25.4% the third time point.

The method for the analysis of OSBs in urine has been described in detail elsewhere [32]. For observations below the limit of detection (LOD) values, we replaced values with LOD/√2. For those with more than 20% of values below LOD (*8-iso-$PGF_{2\alpha}$*, *11-$PGF_{2\alpha}$*, and *15-$PGF_{2\alpha}$*), we ran sensitivity analyses (Supplementary Table 1) by assessing each OSB in three categories: below LOD, above the LOD but below the median or mean (based on biomarker distribution), and above the median or mean. This sensitivity analysis retains LOD data without forcing numeric values. Since the intraclass correlation coefficients (ICC) for OSBs were moderate (0.43–0.66), we examined them in separate, time-point specific models and in a repeated measures model. To account for variability in urine dilution, we adjusted OSB concentrations for gestational timepoint and batch-specific urinary creatinine as previously described [33, 34]. Prior to inferential analyses with EFW, we log-transformed OSBs to stabilize the variance; we interpret estimates for a ln-unit (~2.7x) increase in exposure.

Covariates

We selected potential confounders for our models using a Directed Acyclic Graph (DAG) (Supplementary Fig. 2). First, we reviewed the literature to identify social and biological characteristics that have been associated with both oxidative stress levels and fetal growth [2, 12, 13]. We defined the conditional dependencies between these variables using the DAG, tested covariates for multicollinearity prior to inclusion, and selected the minimally sufficient adjustment set for inclusion as covariates in statistical models. The following covariates, collected by questionnaire, were included in models: pregnant participant's age at enrollment (years), race and ethnicity (White, non-Hispanic/Hispanic/Black, non-Hispanic/Asian/Other or Multiple Race), partnership status (living together/separated or single), education (high school or less/college/post-graduate degree), smoking during pregnancy (yes/no), insurance type (public or private), parity (nulliparous/multiparous), and infant sex. From the electronic health record, we calculated pre-pregnancy body mass index (BMI) using weight (kg) and height (cm). Finally, we also controlled for sample batch to account for non-biological laboratory variation.

Statistical analysis

We summarized participant characteristics, OSBs, and EFW measurements using descriptive statistics. We visually inspected histograms for main variables to examine distribution and spread of data. We then performed linear regression to examine each OSB in relation to EFW at later gestation timepoints in separate models. To better assess directionality of associations, we analyzed OSB levels measured prior to the estimation of fetal weight (e.g., $OSB_{T1} \rightarrow EFW_{T2}$, $OSB_{T1} \rightarrow EFW_{T3}$, $OSB_{T2} \rightarrow EFW_{T3}$). To assess whether OSB levels are differentially associated with fetal weight in smaller versus larger fetuses, we used quantile regression to examine associations between OSBs and EFW at each gestational time period in separate models and generated estimates at the 25th and 75th percentiles of EFW [19, 35].

Next, we fit multiple informant models with generalized estimating equations and specified an interaction between each OSB and exposure timepoint to identify potential windows of heightened susceptibility in relation to EFW at 36 weeks. This approach accounts for the within-person correlation of observations, estimating the population-averaged effect of OSBs on EFW over time. We specified an exchangeable correlation matrix and continuous link function.

All covariates had less than 5% missingness; we imputed the mean for continuous and the mode for categorical variables. We conducted two additional sensitivity analyses: the first restricted to complete cases, the second excluding those with gestational hypertension or gestational diabetes. We used a confidence level of 95% and a false discovery rate correction to account for multiple comparisons [36]. Analyses were conducted in Stata/SE version 15.1.

RESULTS

We describe the characteristics of our analytic sample in Table 1. Approximately half of the sample identified as Hispanic (46.8%), 8.5% as Asian, and 5.4% as non-Hispanic Black. About half of the participants had public insurance (47.5%). A small percentage continued to use tobacco (1.2%) and 11.5% endorsed alcohol use more frequently than once a month during pregnancy. The mean pre-pregnancy BMI was 26.0 kg/m^2 (Standard deviation [SD] = 5.5 kg/m^2). The mean EFW at 20, 30, and 36 weeks was 336.0 (SD = 50.2) grams, 1574.5 (SD = 142.7) grams, and 2833.6 (SD = 262.4) grams, respectively. Table 2 summarizes the measured concentrations of urinary OSBs by study visit and the frequency of values below LOD.

Figure 1 displays effect estimates and 95% confidence intervals from linear regression models examining the relation between OSBs and EFW at a future gestational time point (unadjusted models in Supplementary Table 2). When examining relations between early OSBs (measured < 18 weeks of gestation) and EFW, we found that higher lipid biomarkers *8-iso-PGF2-α* (estimated coefficients: 1.6 g [95% CI: 0.4, 2.7]), 8,15-PGF2-α (2.3 g [95% CI: 1.2, 3.3]), and protein biomarker *diY* (3.4 grams [95% CI: 1.2, 5.6]) were significantly associated with larger EFW at 20 weeks gestation. Higher DNA biomarker *8-OHdG* (–11.6 g [95% CI: –20.1, –3.2]) was associated with significantly smaller EFW at 30 weeks. Early pregnancy *8,15-PGF2-α* lipid biomarker was associated with smaller EFW at 36 weeks (–9.1 g [95% CI: –14.4, –3.7]); whereas *diY* in early gestation was associated with larger EFW at 36 weeks (16.5 g [95% CI: 5.2, 27.8]). Other biomarkers in early pregnancy were not significantly associated with EFW at any timepoint, although a notable trend depicted in Fig. 1 shows that the *diY* biomarker of protein damage was associated with larger EFW across timepoints, even though the association did not reach significance at 30 weeks.

In models examining relations between mid-gestation OSBs (measured 18–25 weeks) and EFW, we found that higher levels of lipid biomarkers *8-iso-PGF2α* (–4.2 g [95% CI: –7.6, –0.9]), *15-PGF2α* (–4.5 g [95% CI: –7.7, –1.2]), *8,15-PGF2α* (–3.9 g [95% CI: –7.0, –0.9]), *MDA* (–12.8 g [95% CI: –21.1, –4.5]), as well as DNA biomarker *8-OHdG* (–20.3 g [95% CI: –27.9, –12.8]) were consistently associated with smaller EFW at 30 weeks. *11-PGF2α* and *diY* also showed an inverse trend with EFW at this timepoint without significance. Mid-gestation lipid biomarkers *15-PGF2α*, *8,15-PGF2α*, and DNA biomarker *8-OHdG* (–9.0 g [95% CI: –15.1, –2.9]; –6.9 [95% CI: –12.6, –1.2]; –17.5 [–31.8, –3.3]; respectively) were associated with significantly smaller EFW at 36 weeks, while protein biomarker *diY* in mid-gestation was not associated with larger EFW (14.0 [95% CI: –0.5, 28.6]).

For OSBs measured in later pregnancy (>25 weeks), only lipid biomarker *11-PGF2α* was associated with smaller EFW at 36 weeks (–8.4 g [95% CI: –13.8, –3.2]).

Figure 2 presents effect estimates and 95% confidence intervals at each output percentile for associations between OSBs and EFW at the 25th and 75th percentile (unadjusted models in Supplementary Table 3). At 30 weeks, for those in the 25th quartile of EFW, we observed consistent associations between OSBs (*8-iso-PGF2α, 11-PGF2α, 15-PGF2α, MDA, 8-OHdG)* and smaller EFW (–5.9 g [95% CI: –10.2, –1.7]; –6.3 g [95% CI: –9.9, –2.7]; –5.2 g [95% CI: –9.3, –1.1]; –19.3 g [95% CI: –30.0, –8.5]; –19.0 g [95% CI: –28.9, –9.2]; respectively). At this 30 week timepoint, we also observed that those in the 75th quartile of EFW, *8-OHdG* was associated with a smaller EFW (–14.4 g [95% CI: –25.9, –3.0]). At 20 weeks for those in the 25th quartile of EFW, *8,15-PGF2-α* was

Table 1. Sample characteristics.

	Total (*N* = 1408) **Variable, *N* (%) or mean (SD)**
Pregnant Participant Characteristics	
Age (years)	32.2 (5.5)
Race and ethnicity	
White	510 (36.3)
Hispanic	657 (46.8)
Black	76 (5.4)
Asian	120 (8.5)
Other or multiple race	42 (3.0)
Education level	
High school or less	422 (30.7)
Some college or college degree	537 (39.1)
Post-graduate degree	414 (30.2)
Partnership status	
Married or living with partner	1,252 (89.4)
Divorced or separated	27 (1.9)
Single or widowed	122 (8.7)
Insurance	
Public	667 (47.5)
Private	736 (52.5)
Employed	924 (66.3)
Pre-pregnancy body mass index	26.0 (5.5)
Parity (Nulliparous)	714 (50.8)
Gestational hypertension	56 (4.0)
Gestational diabetes	208 (14.8)
Alcohol use in pregnancy	159 (11.5)
Tobacco use in pregnancy	17 (1.2)
Recruitment hospital	
NYU Manhattan	768 (54.6)
NYU Brooklyn	385 (27.3)
Bellevue Hospital Center	255 (18.1)
Fetal characteristics	
Fetal sex (female)	680 (48.9)
Estimated fetal weight (grams)[1]	
20 weeks	336.0 (50.2)
30 weeks	1574.5 (142.7)
36 weeks	2833.6 (262.4)

[1]Estimated fetal weight obtained based on clinical ultrasounds with the HadlockIII formula. Predicted estimated fetal weight at 20, 30, and 36 weeks used a linear mixed-effects model assuming nonlinear effects of gestation age.

associated with larger EFW (3.0 g [95% CI: 1.2, 4.8]) as it was in Fig. 1. We did not observe associations at 36 weeks.

Table 3 displays results from our multiple informant models with generalized estimating equations, which included an interaction term between the oxidative stress predictor and biomarker measurement timepoint. We did not detect that any of the exposure windows were associated with EFW at 36 weeks or for 30 weeks (shown in Supplementary Table 4).

Findings were robust to our sensitivity analyses: using categorical values for OSBs, complete case analyses, and models excluding those with gestational diabetes and hypertension.

DISCUSSION

In a longitudinal pregnancy cohort from New York City, we investigated lipid, protein, and DNA biomarkers of oxidative stress in relation to EFW at 20, 30, and 36 weeks. Oxidative stress represents an overload of reactive oxygen species, and has been consistently associated with low birthweight and preterm birth in other studies [10, 13, 16, 28]. We detected the most consistent associations between lipid or DNA biomarkers and smaller EFW at 30 and 36 weeks of pregnancy, particularly in smaller fetuses at the 25th percentile. Contrary to our expectations, we also detected associations between some of our OSBs and larger EFW early in pregnancy. We did not detect specific sensitive windows of exposure influencing EFW. In this community sample, our effect sizes were relatively small but at the population level, small shifts have implications for morbidities associated with fetal size at the tails of the distribution. Our findings advance knowledge about OSBs and fetal weight, framing future lines of inquiry to understand their distinct molecular roles across gestation in the developmental biology of fetal growth, informing future clinical applications to assess oxidative stress exposures [37, 38].

We detected associations between multiple lipid OSBs—which reflect lipid peroxidation and adipose inflammation [6]—and smaller EFW at 30 and 36 weeks of pregnancy. This finding is aligned with prior work, which has detected associations between *8-iso-PGF2α*, an F2-isoprostane generated by the oxidation of arachidonic acid, and decreased fetal growth. One study examining *8-iso-PGF2α* in amniotic fluid early at 15 and 18 weeks found associations with fetal growth restriction as measured by mid-pregnancy (22 to 36 weeks) abdominal circumference [39]. Similarly, in a cohort of preterm deliveries, associations between increased prenatal levels of *8-iso-PGF2α* in urine with decreased anthropomorphic parameters (femur length and head circumference) were observed across all timepoints, but not with fetal weight [13]. In our community-based pregnancy cohort, we detected associations between levels of multiple F2-isoprostane isomers (*8-iso-PGF2α, 15-PGF2α, 8,15-PGF2α*) and smaller EFW at 30 and 36 weeks. These associations were particularly pronounced in those at the 25th percentile of EFW, raising the possibility that oxidative stress plays a role in the growth restriction of smaller fetuses, and a heightened sensitivity within this subgroup.

MDA levels, which reflect the lipid peroxidation of polyunsaturated fatty acids generally rather than arachidonic acid specifically (as the F2-isoprostanes do), are the most abundant OSB found in urine [32]. We detected an association between higher *MDA* in early and mid-pregnancy and smaller EFW at 30 weeks; this was also evident at the 25th percentile. This extends evidence from a prior smaller study ($n = 76$), which detected higher *MDA* in blood samples of pregnant participants with intrauterine growth restriction in comparison to matched controls [11]. *MDA* is not as specific nor as stable as F2-isoprostanes, which may be why we did not detect this association at 36 weeks [40], particularly given the longer lag—potentially up to 10 weeks—between the OSB assessment and 36 week EFW.

While the findings discussed above support our hypotheses about oxidative stress and impaired fetal growth, we also detected

Table 2. Mean concentrations of urinary oxidative stress biomarkers in pregnant people by study visit.

Concentration in urine (ng/m^{-1} [SD])		<18 weeks (ng/m^{-1} [SD])	18–25 weeks (ng/m^{-1} [SD])	>25 weeks (ng/m^{-1} [SD])	% below limits of detection (LOD)
Lipid	8-iso-prostaglandin $F_{2\alpha}$ (8-iso-PGF2α)	0.26 (0.40)	0.27 (0.41)	0.27 (0.44)	30.4%
	11β-prostaglandin $F_{2\alpha}$ (11 − PGF2α)	0.24 (0.55)	0.27 (0.64)	0.24 (0.56)	54.3%
	15(R)-prostaglandin $F_{2\alpha}$ (15 − PGF2α)	0.37 (0.80)	0.40 (0.87)	0.42 (0.75)	32.2%
	8-iso-15(R)-prostaglandin $F_{2\alpha}$ (8,15 − PGF2α)	0.52 (0.89)	0.52 (0.75)	0.60 (0.88)	19.8%
	Malondialdehyde (MDA)	21.0 (17.5)	21.4 (17.3)	20.7 (16.1)	0%
Protein	o,o′−dityrosine (diY)	1.36 (1.52)	1.74 (1.88)	1.68 (1.78)	2.5%
DNA	8−hydroxy−2′−deoxyguanosine (8−OHdG)	3.81 (3.32)	3.51 (7.07)	2.68 (2.61)	0.3%

These concentrations were all further corrected for using the batch and timepoint-specific creatinine to account for minor biological (creatinine) and non-biological (laboratory) variations.

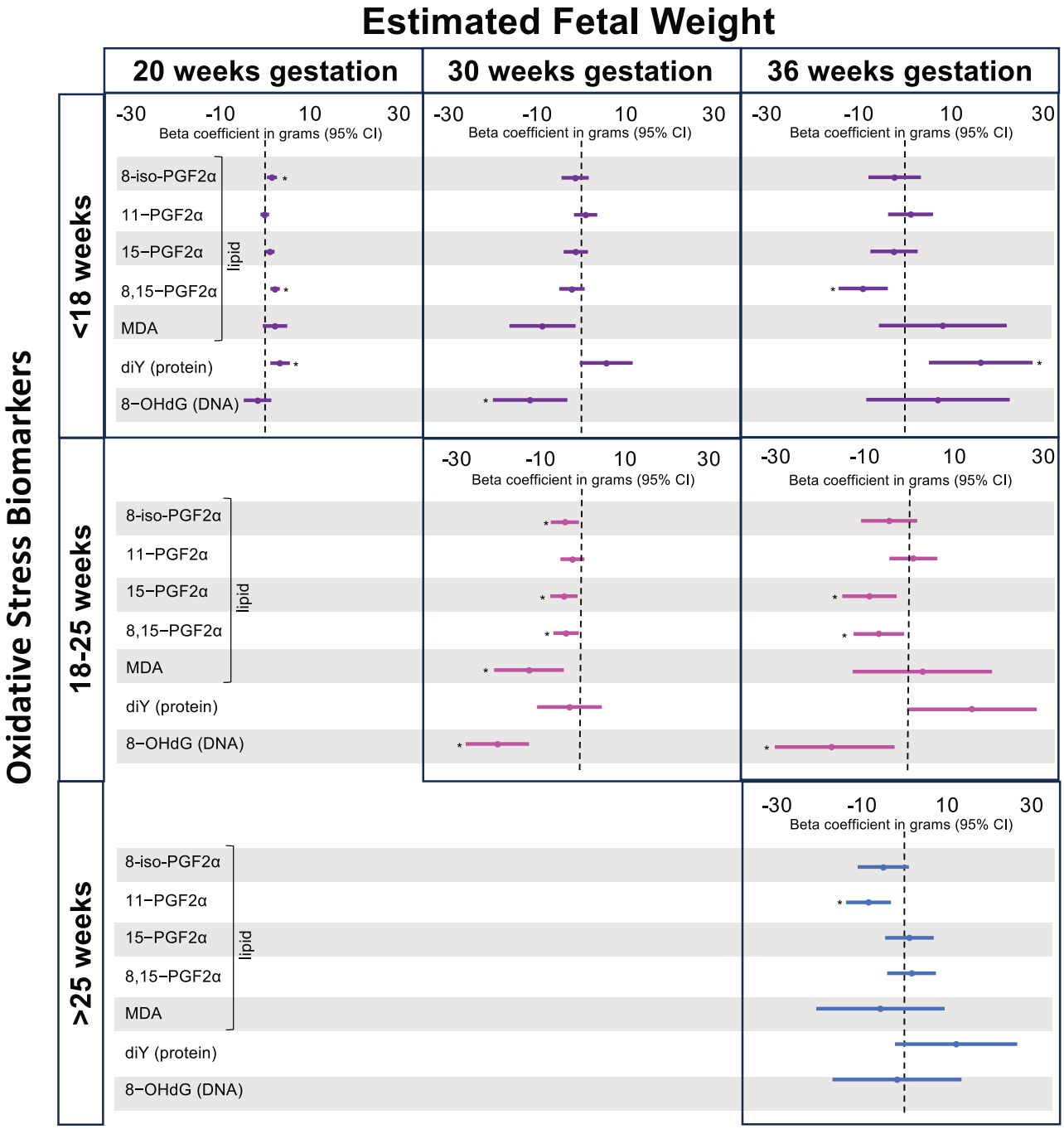

Fig. 1 Change in estimated fetal weight for each ln-unit increase in oxidative stress biomarker. All oxidative stress biomarkers are corrected for creatinine and log-transformed. Full oxidative stress biomarker names are provided in Table 2. Models adjusted for: pregnant participant's age, race, ethnicity, marital status, education, smoking, insurance, parity, fetal sex, pre-pregnancy BMI, laboratory assay batch. Star (*) symbol indicates significance after accounting for multiple comparisons using the effective number of tests method.

significant associations in the reverse direction in early pregnancy: multiple F2-isoprostane lipid biomarkers measured before 18 weeks of pregnancy were associated with larger EFW at 20 weeks of pregnancy. In particular, we observed a shift in the association between *8,15-PGF2α* and EFW across gestational ages, with higher levels associated with larger EFW at 20 weeks but smaller EFW at 36 weeks. Moderate levels of oxidative stress may reflect early critical processes with high energy demands like vascular remodeling. This switch may also reflect reverse causality or residual confounding from maternal inflammation that influences both oxidative stress and fetal growth [13, 41]. While we adjusted for pre-pregnancy BMI, lipid derived oxidative stress is highly prevalent [6] in adipose tissue (which BMI does not completely account for); there may be increased complexity when it comes to obesity-derived vs. other sources of oxidative stress.

In our main analyses, we also found that the protein OSB *diY*, (generated by the oxidation of protein side chains [42, 43]), was associated with larger EFW. While the vast majority of pregnancy studies of protein oxidation focus on damaging effects found in diseases like pre-eclampsia [44], researchers have accumulated additional evidence that protein oxidation has necessary roles in cell survival, possibly through the creation of positive stress

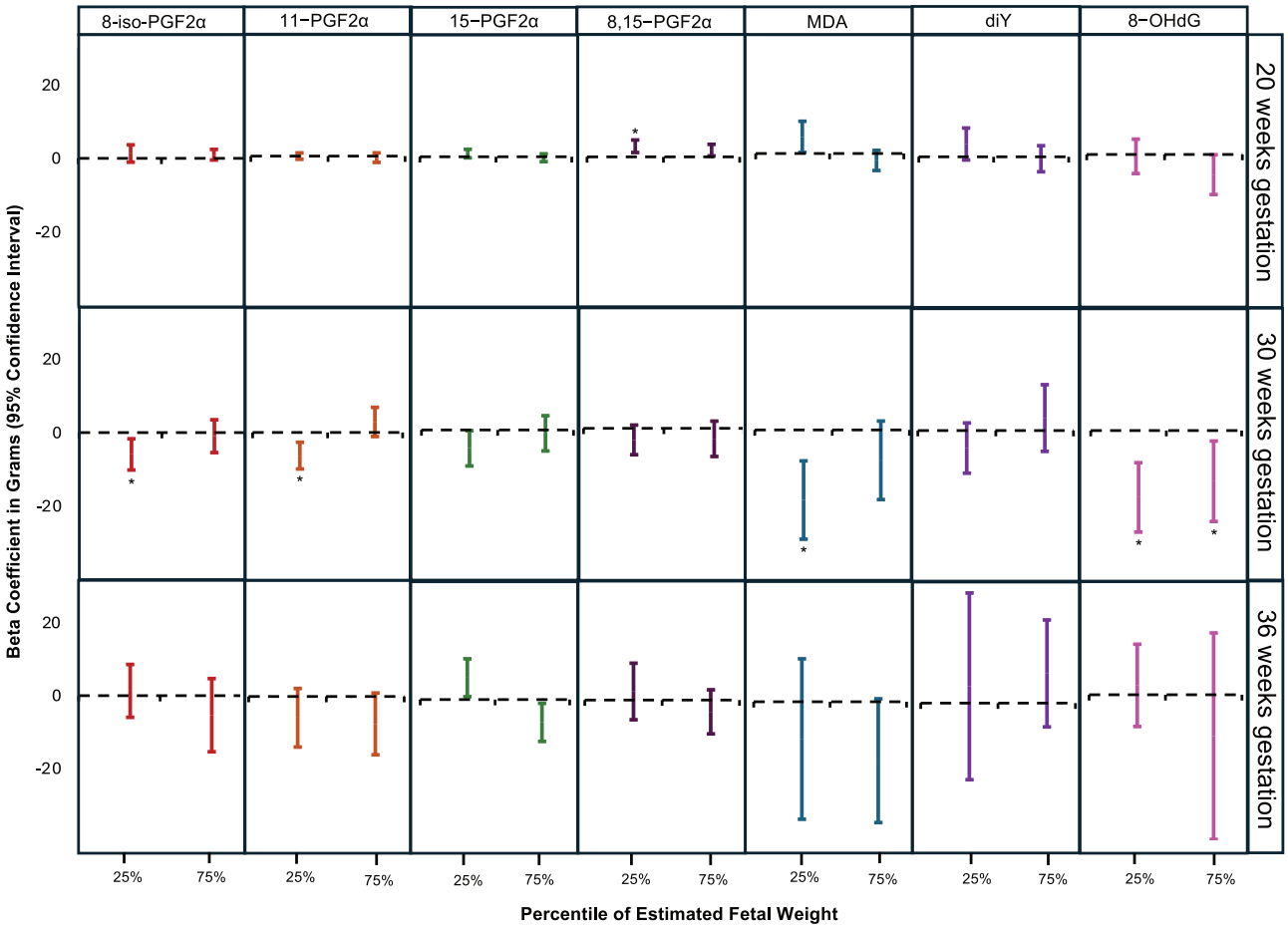

Fig. 2 Change in estimated fetal weight for each ln-unit increase in oxidative stress biomarker at the 25th and 75th percentile. All oxidative stress biomarkers are corrected for creatinine and log-transformed. Full oxidative stress biomarker names are provided in Table 2. Models adjusted for: pregnant participant's age, race, ethnicity, marital status, education, smoking, insurance, parity, fetal sex, pre-pregnancy BMI, laboratory assay batch. Star (*) symbol indicates significance after accounting for multiple comparisons using the effective number of tests method.

situations [45]. Given that markers of tyrosine modification (*diY* is one example of this) have been detected in healthy pregnancies, and that *diY* in particular has a protective association with preterm birth risk [46], protein oxidative stress may have a healthy physiological function [45]. Our cohort was overall a large, diverse, sample of New York City, and oxidative stress levels described were potentially physiological rather than a consequence of a disease process.

We found that *8-OHdG*, our DNA biomarker of nucleic acid oxidation, in early and mid-pregnancy was associated with smaller fetal weight at 30 weeks. Prior work has also identified associations between *8-OHdG* and decreased head circumference, femur length, and low birthweight [12, 13, 47]. Cellular research has also shown that oxidative DNA damage mostly occurs in rapidly growing cells like the trophoblast, the outer layer of the blastocyst embryo, while oxidative lipid damage occurs mostly in the superficial cell layers like the syncytiotrophoblast, which are in direct contact with maternal blood [12, 48]. Understanding the oxidation cell type may help future studies implicate the causes of dysfunction leading to decreased fetal growth. For example, increased levels of lipid oxidative stress may indicate decreased nutrient flow at the interface with maternal blood versus increased DNA oxidative stress may indicate pathology at the trophoblast-blastocyst level [49]. Recognizing these associations in a healthy cohort informs the design of future case control studies that compare types of oxidative stress or serum and urine-based OSBs in disease conditions like preeclampsia or fetal growth restriction to yield additional insights around these processes.

We did not detect evidence of significant windows of sensitivity. Opportunities to improve study design include systematically timing multiple OSB measurements to precede or follow fetal growth measurements to increase causal inference and mechanistic understanding based on our increasing understanding of their relationship.

The primary strength of this study is its large sample size, lending generous power to examine associations between oxidative stress and fetal weight in a community-based sample. Our analysis also included seven measurements of oxidative stress, spanning lipid, protein, and DNA biomarkers, which allows for a more comprehensive assessment of oxidative stress. A key limitation of these findings for future clinical applicability is the variability in detection of OSBs, which may reflect individual differences in oxidative stress burden or assay sensitivity. Potential effects of cryopreservation also cannot be excluded. We conducted sensitivity analyses using categorical variables that supported our main findings. Missing OSB measurements due to loss or follow-up particularly at the second timepoint could introduce selection or information bias, affecting the generalizability of our findings. We only indirectly accounted for lifestyle characteristics that likely affect oxidative stress like physical activity and diet through body mass index. The overall risk of pregnancy complications can be estimated through smoking and alcohol use rates, though rates are comparable to U.S. national

Table 3. Repeated-measures models of oxidative stress and estimated fetal weight at 36 weeks: moderation with time.

Oxidative Stress Biomarker		Estimate at <18 weeks B grams (95% CI)	Estimate at 18–25 weeks[a] B grams (95% CI)	Estimate at >25 weeks[a] B grams (95% CI)
Lipid	8-iso-PGF2α	−0.02 (−1.3, 1.2)	−0.01 (−1.3, 1.3)	−0.03 (−1.3, 1.2)
	11 − PGF2α	−0.02 (−1.0, 0.9)	−0.01 (−1.05, 1.03)	−0.06 (−1.1, 1.0)
	15 − PGF2α	−0.06 (−1.2, 1.1)	−0.06 (−1.3, 1.2)	−0.03 (−1.2, 1.2)
	8,15 − PGF2α	−0.07 (−1.2, 1.1)	−0.04 (−1.2, 1.1)	−0.03 (−1.2, 1.2)
	MDA	0.04 (−3.1, 3.2)	0.04 (−3.4, 3.4)	0.09 (−3.1, 3.3)
Protein	diY	0.08 (−2.2, 2.4)	0.1 (−2.3, 2.5)	0.08 (−2.4, 2.5)
DNA	8−OHdG	−0.02 (−3.4, 3.4)	−0.07 (−3.0, 2.9)	−0.03 (−3.3, 3.3)

Generalized estimating equations with an interaction term defined for exposure and exposure timing to assess associations between repeated measures of oxidative stress and estimated fetal weight at 36 weeks. All oxidative stress biomarkers are corrected for creatinine and log-transformed. Full oxidative stress biomarker names are provided in Table 2. Models adjusted for: pregnant person's age, race, ethnicity, partnership status, education, smoking, insurance, parity, fetal sex, pre-pregnancy BMI, laboratory assay batch.

averages [50]. Future studies may consider collecting this data over time, as habits may change throughout pregnancy. While our high quality ultrasound data was collected by licensed sonographers, we did not have the indications for the clinical ultrasounds. Most of our sample had late pregnancy scans, reflecting an older sample (mean age ~31), or more frequent ultrasound practices at an academic medical center. We excluded scans beyond the 90th percentile of ultrasound visits among the sample to minimize bias, which could go in either direction as indications for additional ultrasound could bias for larger (e.g., gestational diabetes) or smaller (e.g., intrauterine growth restriction) fetuses.

CONCLUSION

This study describes associations between prenatal levels of lipid, protein, and DNA OSBs and subsequent EFW in a pregnancy cohort from the general NYC population. We detected associations between higher levels of OSBs (lipid and DNA) and smaller EFW at 30 and 36 weeks of pregnancy, particularly for fetuses at the 25th percentile. Protein OSB earlier in pregnancy was associated with larger EFW. These findings contribute to our understanding of oxidative damage and its potential life course consequences.

DATA AVAILABILITY

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

CDL was responsible for the conceptualization and design of the study, performed a portion of the statistical analysis, and prepared the original draft. LT contributed to conceptualization, provided resources and supervision, secured funding acquisition, and participated in writing (review and editing). AG contributed to the conceptualization, provided resources and supervision, secured funding acquisition, and participated in writing (review and editing). AG also contributed to the statistical analysis and data curation. WC contributed to the methodology, the statistical analysis, and participated in writing (review and editing). ML, SS, KAP, SEL, YW, and WY all contributed substantially to the statistical analysis, data curation, and refinement of the statistical methodology. YA assisted with data curation, provided resources, and contributed to project administration. SML provided clinical expertise, contributed resources, and participated in writing (review and editing). KK was responsible for the formal analysis related to chemicals/lab analysis, performed validation, provided resources, and participated in writing (review and editing). All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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