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Urinary oxidative stress biomarkers and accelerated time to spontaneous delivery

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Abstract

Background: Oxidative stress has been implicated in numerous birth outcomes, including spontaneous preterm birth. However, the relationship with presentation at delivery has been less

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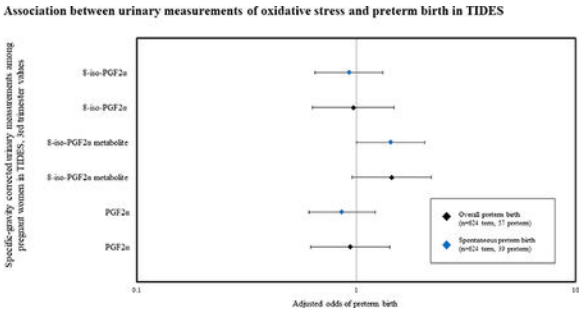
well studied. We assessed the relationship between oxidative stress biomarkers and gestational duration with a focus on spontaneous presentation for delivery.

Methods: Our sample included 740 women from a multi-center prospective cohort study, recruited from 2010–2012. Resultant measures of oxidative stress in pregnancy prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$), and the primary 8-iso-$PGF_{2\alpha}$ metabolite were measured in third trimester urine samples. Information on presentation for delivery was abstracted from medical records. We examined associations with preterm birth using adjusted logistic models. Time to event (overall delivery and spontaneous delivery) was examined using adjusted accelerated failure time models.

Results: The 8-iso-$PGF_{2\alpha}$ metabolite was associated with increased odds of overall preterm birth (OR: 1.44 [95% CI: 1.00, 2.06]), and the association with spontaneous preterm birth was similar in magnitude but not statistically significant (OR: 1.45 [95% CI: 0.96, 2.20]). We did not detect associations between other biomarkers and preterm birth, or between biomarkers and timing of overall or spontaneous delivery in accelerated failure time models.

Conclusions: Our data suggest that increased oxidative stress, as indicated by the 8-iso-$PGF_{2\alpha}$, may be associated with preterm birth. In contrast to previous studies, associations were similar among individuals with spontaneous versus non-spontaneous presentation for delivery.

Graphical abstract



Keywords

oxidative stress; isoprostanes; prostaglandin; preterm birth; spontaneous labor

Introduction

Timing of delivery is a key factor for infant survival and subsequent health of the child. Preterm birth and associated low birthweight accounted for 17% of all infant deaths in 2015 and complications from preterm birth are the leading cause of death for children under 5 worldwide [1, 2]. Preterm babies who survive may have short- or long-term health complications [1].

Oxidative stress is the biological imbalance between free radicals and antioxidant defenses. It can damage biomolecules, interrupt important signaling pathways, and has been implicated in a number of adverse birth outcomes [3–5]. Specifically, previous research has suggested an association between maternal oxidative stress biomarkers and increased risk of

preterm birth or shorter gestational duration, although results remain inconclusive [6–11]. This ambiguity may be the consequence of heterogeneity in the outcome or differences in timing and markers used to measure oxidative stress.

Previous work by Ferguson et al. demonstrated that the urinary oxidative stress biomarker 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) was associated with increased odds of preterm birth with spontaneous presentation specifically (defined as delivery prior to 37 weeks with presentation of spontaneous labor or preterm premature rupture of membranes [PPROM]) [6]. PPROM is the premature rupture of membranes (PROM) occurring prior to 37 weeks gestation. The association between oxidative stress and spontaneous labor is thought to be a result of premature senescence of the tissues and membranes in the maternal-fetal compartment [12]. It remains unclear whether the mechanism leading to the initiation of delivery plays a role in term as well as preterm pregnancies. Thus, in this new cohort with additional biomarkers, our aim was to replicate our previous findings of an association between oxidative stress biomarkers and spontaneous preterm birth and also to investigate whether oxidative stress was associated with accelerated time to a spontaneous delivery *regardless of whether the delivery was preterm*.

The second objective of our study was to augment the understanding of this relationship by measuring two additional biomarkers of oxidative stress. In addition to 8-iso-$PGF_{2\alpha}$ we measured its primary metabolite and prostaglandin-$F_{2\alpha}$ ($PGF_{2\alpha}$). The 8-iso-$PGF_{2\alpha}$ metabolite may be a superior marker of systemic oxidative stress than 8-iso-$PGF_{2\alpha}$ itself [13]. $PGF_{2\alpha}$, when measured simultaneously with 8-iso-$PGF_{2\alpha}$, may enable distinction of the intertwined oxidative stress and inflammation pathways [14]. Furthermore, although $PGF_{2\alpha}$ has also been associated with inflammatory pathways and mechanisms underlying preterm birth [15], no previous epidemiologic studies have examined its association with gestational age at delivery.

Methods

Study population

The Infant Development and Environment Study (TIDES) is an ongoing prospective cohort of pregnant women recruited from four academic prenatal clinics: University of California, San Francisco (UCSF); University of Rochester Medical Center (URMC); University of Minnesota (UMN); and University of Washington/Seattle Children's Hospital (UW/SCH). Details on TIDES study design and methods have been previously published [16]. Women were recruited between August 2010 and August 2012 and were eligible if they were <13 weeks pregnant, aged 18 or older, able to read and write English (or Spanish at UCSF), and did not have a medically threatened pregnancy. During three routine prenatal visits, women completed a questionnaire and provided a spot urine sample. Oxidative stress markers were measured in urine collected at visit 3 (median: 32.1 weeks; interquartile range: 30.4, 34.6). For the present study, we included women with data on oxidative stress markers from visit 3 and gestational age at delivery. Multiple pregnancies were excluded from this analysis.

Study protocols were approved by IRBs at each data collection institution and at the Icahn School of Medicine at Mount Sinai, which has served as the TIDES Coordinating Center

since 2011. All participants provided signed informed consent before starting any study activities.

Oxidative stress biomarker analysis

Urine samples were collected in sterile specimen cups and immediately analyzed for urinary specific gravity, an indicator of urine dilution, using a hand-held refractometer. Specific gravity is thought to be a better measure of hydration status during pregnancy than creatinine due to its improved within-person reproducibility and lower amount of systematic variation [17]. Samples were then stored at −80° C prior to shipment to Vanderbilt Eicosanoid Core Laboratory for measurement of oxidative stress biomarkers. Urinary concentrations of the following compounds were measured using gas chromatography-negative ion chemical ionization-mass spectrometry employing stable isotope dilution: free 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$), its major metabolite 2,3-dinor-5,6-dihydro-15-F_{2t}-isoprostanes, and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). $PGF_{2\alpha}$ is derived from the same parent compound as F_2-isoprostanes and is also thought to be involved in inflammatory conditions [18]. Further analytic details are described elsewhere [19]. The coefficients of variation were 7.7% for 8-iso-PGF2α, 10% for 8-iso-PGF2α metabolite, and 12% for PGF2α.

Measured values of 8-iso-$PGF_{2\alpha}$ can be divided into a chemical and an enzymatic fraction, where the chemical fraction reflects concentrations produced from lipid peroxidation and the enzymatic fraction is generated from prostaglandin-endoperoxide synthases, a result of inflammation [21, 22]. Quantification of the enzymatic and chemical fractions of 8-iso-$PGF_{2\alpha}$ was determined using the 8-iso-$PGF_{2\alpha}$ to $PGF_{2\alpha}$ modeled ratio as described by van ‘t Erve et al. [14] and as calculated by a custom interface for the R package Constrained Linear Mixed Effects [23]. There are no reference values for the fractions because the proportions are dependent on the situation-specific production of 8-iso-$PGF_{2\alpha}$.

All oxidative stress biomarker measures were natural log-transformed after correction for urinary specific gravity using the following formula: $O_c = O[((1.014 - 1) / Sg - 1)]$ where O_c = specific gravity-corrected oxidative stress biomarker concentrations, O = measured oxidative stress biomarker concentrations, 1.014 is the mean of specific gravity among all TIDES samples analyzed, and Sg is the specific gravity measured in that sample [24].

Gestational age and presentation at delivery

Gestational age at delivery was assessed by first available ultrasound or, if no ultrasound was available, the physician’s estimate of gestational age at birth. Data on clinical presentation at delivery were abstracted from participants’ medical records. Double abstraction was performed by an independent abstractor for approximately 10% of records. The double-abstracted files were compared for accuracy and for identification of any potentially unreliable variables, indicating systematic errors in abstraction of that variable. The variables included in this analysis had high consistency between abstractors. Where disagreement occurred, a rule was created to reconcile data points. If one abstractor noted an outcome while the other did not, we included the outcome as we thought it was more plausible that one abstractor would miss it rather than the other falsely identifying it. For example, if one abstractor recorded PROM but the other abstractor did not, that woman was

considered to have experienced PROM. The primary data abstracted for this analysis included clinical conditions at admission for delivery, as recorded by physicians, in combination with ICD10 codes. Spontaneous labor was diagnosed using ICD codes o60.1 and o60.2. For diagnosis of PROM and PPROM, we used ICD code o42 and date of diagnosis.

The primary outcomes of interest in this study were time to any delivery and time to spontaneous delivery. Spontaneous delivery was defined as delivery preceded by presentation with spontaneous labor or PROM [6]. As a secondary analysis, we additionally examined time to delivery by PROM alone. There were a number of women who were recorded to have experienced both PROM and spontaneous labor. In all cases, PROM either preceded spontaneous labor or occurred on the same day.

Statistical Analysis

Covariates were identified through a literature review and possible confounders were identified with the use of a Directed Acyclic Graph. These confounders were evaluated in our sample using stepwise selection. The final model included maternal age at delivery (continuous), pre-pregnancy body mass index (BMI) (continuous, kg/m^2), maternal race (White, Black, Other), specific gravity, and gestational age at sample collection. Other covariates such as education, smoking, gestational diabetes, alcohol consumption, and study center were considered but not included in final models due to minimal effects on parameter estimates. In our population, numbers of women supplementing with antioxidants in the 3^{rd} trimester were low (Vitamin A: 2 women; Vitamin E: 3 women) and thus these variables were not included as covariates. All demographic information was self-reported; BMI was calculated from self-reported height and pre-pregnancy weight. Additionally, we standardized all oxidative stress measures to the population's interquartile range (IQR) so that model outputs were per IQR increase.

We explored population demographics and associations between these characteristics and gestational age at birth and potential differences in demographics by study center. We performed a bivariate analysis to demonstrate crude differences in oxidative stress biomarkers in the population overall and by preterm versus term births.

To compare results with this study to previous work by Ferguson et al., we investigated the association between oxidative stress markers and preterm birth (delivery <37 weeks of gestation) and spontaneous preterm (delivery <37 weeks of gestation with presentation of spontaneous labor or PPROM) in adjusted logistic models.

Cox proportional hazards models yield a measure of association between exposure and a binary outcome that is time-dependent, but they do not provide any information on change in time to event. Accelerated failure time models yield the percent reduction in time to a specific event in association with a unit increase in exposure [25]. This is particularly valuable in the study of time to spontaneous delivery, when censoring for other presentations at delivery is necessary. The accelerated failure time model allows individuals who deliver with other presentations (e.g., scheduled C-section, induction) to contribute time up until their delivery without excluding them from the model. Interpretations of effect estimates

from accelerated failure time models are also straightforward. In the context of this analysis, an effect estimate of - 10% would indicate that women with biomarker levels in the 75th percentile experience the event (e.g., spontaneous delivery) 10% sooner than women with concentrations in the 25th percentile. For a full pregnancy (280 days), this percent decrease corresponds to the outcome occurring 28 days earlier.

In our study, we created accelerated failure time models for oxidative stress markers in relation to: 1) time to any delivery; and 2) time to spontaneous delivery (presentation with spontaneous labor and/or PROM leading to delivery). As a secondary analysis, we also examined time to delivery with presentation of PROM only, which is a spontaneous presentation but may be considered a complication of pregnancy at any gestational age (whereas spontaneous labor is not). For models of spontaneous delivery and PROM, women who had a delivery without the presentation of interest were censored at the date of delivery. Analyses were performed using SAS 9.4 (Cary, NC).

Results

The study population included 740 women who were primarily White, married, multiparous, of normal pre-pregnancy BMI, and had at least some college education (Table 1).

Gestational duration was shorter in women who had higher BMI, who were single, who had less education, and who had lower incomes. Gestational duration was also shorter for women with a higher number of previous pregnancies and for women with previous preterm births. Women at URMC had shorter gestational duration than at the other sites and were more likely to be overweight, Black, to smoke during pregnancy, and to have less education and lower income (Supplemental Table 1).

Among the 740 women, 423 (57.2%) had spontaneous labor and/or PROM as the reason for presentation at delivery (Figure 1).

Of these, 67 (15.8%) had PROM only. There were 22 women (5.20%) who experienced both PROM and spontaneous labor. After separating individuals into preterm (<37 weeks) and term (>=37 weeks), 67% (n=41) of preterm births and 56% (n=382) term births were considered spontaneous (Figure 1). Alternative reasons for presentation at delivery included preeclampsia, intrauterine growth restriction, and “other” presentations such as scheduled or induced delivery or vaginal bleeding. A small number of preterm (n=2) and term (n=56) individuals were missing information on presentation at delivery. All individuals with other or missing presentations were censored at birth for accelerated failure time models of spontaneous delivery or PROM. 59 women were missing information on relevant covariates and were excluded from multivariable analyses.

Levels of the oxidative stress biomarkers differed by timing of delivery for the 8-iso-$PGF_{2\alpha}$ metabolite only (Table 2).

Levels of the metabolite were statistically higher among women who delivered preterm compared to women who delivered term (Geometric mean [95% CI] preterm: 0.75 ng/mL

[0.67, 0.84] vs. term: 0.64 ng/mL [0.62, 0.66]), p=0.01. There were no other statistically significant differences between chemicals among women who delivered preterm and term.

Adjusted associations between chemical concentrations and overall preterm birth were generally null except for the 8-iso-$PGF_{2\alpha}$ metabolite, where an IQR increase in concentration was associated with an odds ratio (OR) of 1.44 [95% confidence interval (CI): 1.00, 2.06], p=0.05 (Table 3).

The metabolite was also associated with increased odds of spontaneous preterm birth but the association was not statistically different (OR: 1.45 [95% CI: 0.96, 2.20]) p=0.08.

In the multivariable accelerated failure time models, there were no associations between oxidative stress biomarkers and time to any delivery or time to spontaneous delivery (Table 4). For the 8-iso-$PGF_{2\alpha}$ metabolite, an IQR difference was associated with a 0.19% shorter gestational age [95% CI: −0.50, 0.12], corresponding to approximately 0.5 days shorter gestation. In our secondary analysis of time to delivery with presentation of PROM only, we observed that $PGF_{2\alpha}$ was associated with a 0.97% decrease in gestational age [95% CI: −2.27, 0.34], which corresponds to delivery approximately 3 days earlier when comparing women in the 75th percentile of exposure to women in the 25th percentile. However, this difference did not reach statistical significance. No associations were observed with 8-iso-$PGF_{2\alpha}$ (ß=0.18% [95% CI: −1.21, 1.57]) or the 8-iso-$PGF_{2\alpha}$ metabolite (ß=0.21 [95% CI: −1.20, 1.62] and timing of delivery among women with PROM.

The second objective of our analysis was to distinguish the enzymatic and chemical fractions of 8-iso-$PGF_{2\alpha}$, representing generation by the inflammation pathway compared to production from the oxidative stress pathway, respectively. However, because we did not observe associations with the 8-iso-$PGF_{2\alpha}$ parent compound, associations with each fraction are not interpretable and thus were not calculated.

Discussion

In this analysis examining urinary oxidative stress biomarker levels in relation to timing of delivery, we observed an association between a metabolite of 8-iso-$PGF_{2\alpha}$ and preterm birth, but associations were attenuated in models restricted to spontaneous preterm births. No associations between 8-iso-$PGF_{2\alpha}$ or $PGF_{2\alpha}$ and preterm or spontaneous preterm birth were detected. Additionally, while we hypothesized that there would be an association between oxidative stress and timing of spontaneous delivery, regardless of whether that delivery was preterm, that was not the case in our study population; no associations between oxidative stress biomarkers and time to delivery overall or to spontaneous delivery were observed in accelerated failure time models.

The association between oxidative stress and timing of delivery is an important pathway to study. Previous studies have shown that environmental chemicals have been associated with oxidative stress levels, so oxidative stress represents an at least partially modifiable risk factor [26, 27].

Ferguson et al. previously measured total urinary 8-iso-$PGF_{2\alpha}$ levels at up to four points across pregnancy in a case-control study of preterm birth (n=130 cases, n=352 controls) [6]. They identified strong associations between 8-iso-$PGF_{2\alpha}$ concentrations averaged over pregnancy and prematurity, driven by associations between oxidative stress levels and spontaneous preterm birth specifically (OR: 6.25 [95% CI: 2.86, 13.7]). Our findings are in contrast to this study, as we observed no association between 8-iso-$PGF_{2\alpha}$ and preterm birth or spontaneous preterm birth. Other epidemiologic studies of the relationship between oxidative stress biomarkers and gestational age at delivery or preterm birth have differed by biomarker, analytic method, timing of measurement in pregnancy, and matrix (i.e., blood, urine, or amniotic fluid) [7–10, 28, 29]. Two of the other four studies examining 8-iso-$PGF_{2\alpha}$ identified an association with reduced time to delivery [9, 11, 28, 29].

8-iso-$PGF_{2\alpha}$ produced in the intrauterine compartment is likely the most biologically relevant for the associations observed with timing of delivery; however, it is not possible to discern the contribution of this compartment to measured urinary 8-iso-$PGF_{2\alpha}$ in this or any other human study. Total 8-iso-$PGF_{2\alpha}$ may be a better indicator of uterine 8-iso-$PGF_{2\alpha}$, as it is largely composed of the glucuronidated 8-iso-$PGF_{2\alpha}$. In urine, glucuronidated 8-iso-$PGF_{2\alpha}$ reflects formation throughout the body as opposed to free 8-iso-$PGF_{2\alpha}$ which is formed directly in the kidney [30]. In our study, free 8-iso-$PGF_{2\alpha}$ was measured as opposed to total (i.e., free and glucuronidated) 8-iso-$PGF_{2\alpha}$ which was used by Ferguson et al. Thus, while our study utilized mass spectrometry, which is more specific than the enzyme immunoassay used in that study [31], it is possible that our measure was less efficient at capturing 8-iso-$PGF_{2\alpha}$ levels in the compartment of interest.

In addition to 8-iso-$PGF_{2\alpha,}$ we measured its metabolite which was associated with preterm birth. Direct kidney synthesis does not significantly affect concentrations of this compound, as metabolism is required prior to excretion in the urine which occurs mainly in organs such as the lung and liver [32, 33]. Since 8-iso-$PGF_{2\alpha}$ formed in the kidney is immediately excreted, the contribution of metabolite from this organ is minimal. Therefore, the 8-iso-$PGF_{2\alpha}$ metabolite may better reflect contributions from the whole body including the uterus. This may explain why we observed associations between the metabolite, but not 8-iso-$PGF_{2\alpha}$, and preterm birth.

In addition to the epidemiologic evidence provided by previous human studies, animal and *in vitro* evidence supports the hypothesis that oxidative stress would be associated with shortened gestation specifically among individuals with a spontaneous presentation at delivery. Oxidative stress in the maternal-fetal compartment could induce upregulation of the signaling cascade that precipitates the initiation of spontaneous labor [34]; alternatively, or in addition, it could cause accelerated senescence of the maternal-fetal membranes resulting in PROM [12]. The association we observed between the 8-iso-$PGF_{2\alpha}$ metabolite and spontaneous preterm birth was similar in magnitude to the association with overall preterm birth, but had a wide confidence interval. This attenuation of effect size could be attributed to the small number of cases of spontaneous preterm birth in this population (n=41). We additionally expected to observe an association with accelerated time to spontaneous delivery, regardless of whether or not the delivery was preterm, but this was not the case in accelerated failure time models. This may indicate that the pathologic relationship between

oxidative stress and shortened gestation is specific to preterm birth and does not have a major impact on deliveries after 37 weeks gestation. Indeed, it has been posited that the factors contributing to the onset of labor are very different in these two groups [35].

We additionally examined associations between oxidative stress and accelerated time to PROM specifically in a secondary analysis. Based on the biologic data, oxidative stress-induced premature senescence of the tissues and membranes in the maternal-fetal compartment is likely to be the most important mechanism connecting oxidative stress to preterm birth [12]. Thus, we would expect to observe associations with this presentation specifically. When we separated spontaneous labor from PROM, we found that an increase in concentrations of $PGF_{2\alpha}$ was associated with onset of PROM approximately 3 days earlier, although this association was not statistically significant. Like 8-iso-$PGF_{2\alpha}$, $PGF_{2\alpha}$ is derived from arachidonic acid [18] and is known to mediate inflammatory responses across the body and during labor. More specifically, levels have been associated with contraction of the smooth muscle of the uterus and cervical ripening [15]. Since $PGF_{2\alpha}$ can also contribute to 8-iso-$PGF_{2\alpha}$ levels, traditionally thought to reflect oxidative stress only [14], this could indicate that previously observed associations between oxidative stress markers and early delivery may be driven in part by upregulation of inflammatory pathways that are detected by oxidative stress markers. This question deserves additional exploration in a study with an expanded sample size and prospective assessment of PROM in pregnancy.

Our study is not without limitations. Conditions such as preeclampsia and fetal growth restriction are associated with increased oxidative stress levels and may have led to a scheduled delivery or non-spontaneous delivery. Women with a scheduled or non-spontaneous delivery were censored in our analysis, but those outcomes may represent competing risks rather than administrative censoring. Although we have evidence that the data were abstracted accurately and medical record abstraction is the gold standard for ascertainment, we cannot rule out the possibility of misreporting of outcomes and diagnosis dates by physicians. It is difficult to predict in which direction this may bias our results. Additionally, approximately 50% of women in our sample had spontaneous labor. Although little data exists on rates of spontaneous labor in the general population, this low percentage may reflect poor documentation within the medical records. One study of nearly 20 million U.S. births found that the spontaneous preterm delivery rate was 4.5% in 2012, comparable with our rate of 5.5% in this analysis [36]. Additionally, there is not always a clear distinction between types of preterm birth (medically indicated, spontaneous preterm labor, and PPROM) [37]. It is often impossible to determine if the rupture of membranes preceded spontaneous labor when women present for delivery [37].

There are many strengths to this study. Beyond just measuring 8-iso-$PGF_{2\alpha}$, we were able to examine additional biomarkers that enable more precise evaluation of oxidative stress pathways leading to the outcomes of interest. Use of 8-iso-$PGF_{2\alpha}$ is preferred over use of other biomarkers of oxidative stress such as malondialdehyde (MDA) or 8-hydroxydeoxyguanosine (8-OHdG). MDA is produced from reactions other than lipid peroxidation, and has low stability due to rapid enzyme degradation and its high tendency to react with other proteins [38]. Quantification of 8-OHdG can differ meaningfully based on method, and substantial variability due to human sources (e.g., urine composition, sampling

timepoint) have been noted [39]. In contrast, F_2-isoprostanes are chemically stable over time, specific to peroxidation, and reliable [40]. Measuring concentrations in urine rather than in plasma allowed us to avoid autoxidation during storage, a concern with plasma measurements [41].

Additionally, we looked at more specific outcomes than just gestational age or preterm birth to isolate spontaneous events of delivery from induction or medically indicated deliveries. We also innovatively applied an accelerated failure time model to address our research questions, which allows for use of all available information and provides easily interpretable effect estimates (percent reduction in gestational age at delivery). However, accelerated failure time models are less flexible to distributional misspecification than Cox models [42].

Conclusions

We observed modest associations between the 8-iso-$PGF_{2\alpha}$ metabolite and preterm birth but we did not observe associations with spontaneous preterm birth specifically. Furthermore, we did not observe associations with the markers measured and time to any delivery or spontaneous delivery, which might suggest that this mechanism has less of a role in the initiation of labor at term. Future research on this topic should focus on accurate ascertainment of outcomes for more clear delineation of the role of oxidative stress and inflammation in relation to gestational duration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

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Abbreviations:

$PGF_{2\alpha}$	prostaglandin $F_{2\alpha}$
8-iso-$PGF_{2\alpha}$	8-iso-prostaglandin $F_{2\alpha}$
OR	odds ratio
CI	confidence interval
PPROM	preterm premature rupture of membranes
PROM	premature rupture of membranes
TIDES	The Infant Development and Environment Study

UCSF	University of California, San Francisco
URMC	University of Rochester Medical Center
UMN	University of Minnesota
UW/SCH	University of Washington/Seattle Children's Hospital
BMI	body mass index
IQR	interquartile range
GM	geometric mean
MDA	malondialdehyde
8-OHdG	8-hydroxydeoxyguanosine

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Highlights

- 8-iso-PGF2α metabolite associated with increased odds of preterm birth
- 8-iso-PGF2α metabolite associated with increased odds of spontaneous preterm birth
- No association with oxidative stress biomarkers and accelerated time to delivery

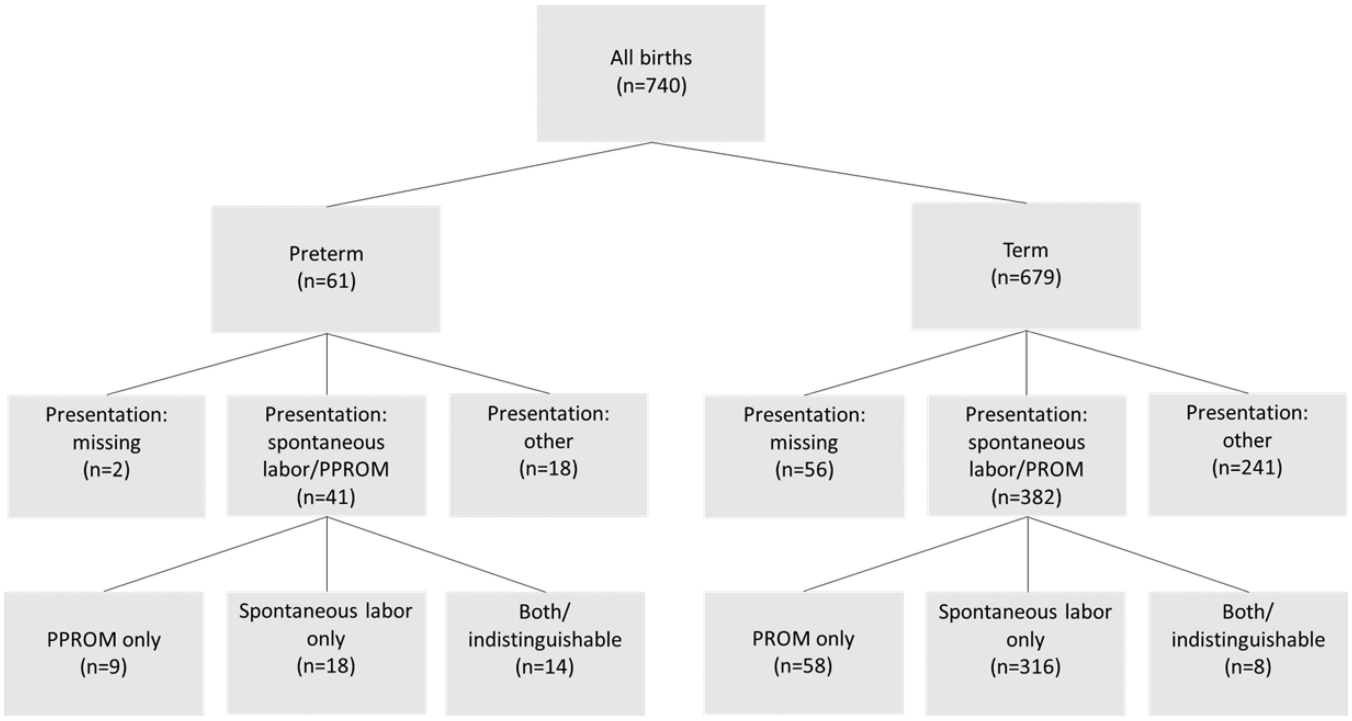

Figure 1.

Reason for presentation at hospital for delivery in women who delivered preterm (<37 weeks) and term (>=37 weeks) in The Infant Development and the Environment Study (TIDES).

Abbreviations: preterm premature rupture of membranes (PPROM); premature rupture of membranes (PROM)

Table 1.

Characteristics of study population (n=740)

	N (%)	Gestational age at delivery (weeks) Mean (SD)	p-value[a]
Maternal age, years			
<25	94 (12.7)	39.1 (1.7)	0.17
25–29	149 (20.1)	39.4 (1.8)	
30–34	241 (32.6)	39.5 (1.6)	
≥35	201 (27.2)	39.4 (1.6)	
Missing	55 (7.4)		
Pre-pregnancy BMI, kg/m^2			
<18.5	16 (2.2)	40.0 (1.2)	0.01
18.5 – 24.99	412 (55.7)	39.5 (1.5)	
25 – 29.99	159 (21.5)	39.4 (1.6)	
≥30	144 (19.5)	39.0 (2.0)	
Missing	9 (1.2)		
Race			
White	506 (68.4)	39.4 (1.6)	0.20
Black	96 (13.0)	39.1 (1.9)	
Other	137 (18.5)	39.5 (1.5)	
Missing	1 (0.1)		
Hispanic/Latino			
No	666 (90.0)	39.4 (1.6)	0.55
Yes	66 (8.9)	39.3 (1.6)	
Missing	8 (1.1)		
Smoking			
None	686 (92.7)	39.4 (1.6)	0.86
Any	41 (5.5)	39.3 (1.6)	
Missing	13 (1.8)		
Alcohol			
None	698 (94.3)	39.4 (1.7)	0.39
Any	29 (3.9)	39.6 (1.2)	
Missing	13 (1.8)		
Marital status			
Married/living together	617 (83.4)	39.5 (1.6)	<0.01
Single	121 (16.4)	39.0 (1.9)	
Missing	2 (0.3)		
Education			
High school or less	103 (13.9)	39.0 (1.7)	<0.01
Any college/tech school	317 (42.8)	39.2 (1.7)	
Any graduate work	314 (42.4)	39.7 (1.5)	
Missing	6 (0.8)		

	N (%)	Gestational age at delivery (weeks) Mean (SD)	p-value[a]
Income			
<25k	173 (23.4)	39.0 (1.9)	<0.01
25–65k	142 (19.2)	39.4 (1.5)	
>65k	400 (54.1)	39.5 (1.6)	
Missing	25 (3.4)		
Infant sex			
Male	357 (48.2)	39.4 (1.6)	0.52
Female	383 (51.8)	39.4 (1.7)	
Missing	0 (0)		
Duration of pregnancy[b]			
Preterm birth	61 (8.2)	35.5 (1.2)	<0.01
Term birth	679 (91.8)	39.7 (1.2)	
Missing	0 (0)		
Study center			
UCSF	185 (25.0)	39.6 (1.6)	<0.01
UMN	202 (27.3)	39.3 (1.7)	
URMC	210 (28.4)	39.1 (1.7)	
UW	143 (19.3)	39.8 (1.4)	
Missing	0 (0)		
Previous pregnancies			
0	280 (37.8)	39.6 (1.6)	0.04
1–3	369 (49.9)	39.4 (1.7)	
4–6	73 (9.9)	39.0 (1.6)	
Missing	18 (2.4)		
Prior preterm birth[c]			
Yes	61 (8.2)	38.3 (1.9)	<0.01
No	679 (91.8)	39.5 (1.6)	
Missing	0 (0)		

[a] P-value was calculated using either ANOVA or t-test testing differences in gestational age across demographic categories.

[b] Preterm birth is defined as birth after less than 37 weeks gestation. Term birth is birth after at least 37 weeks gestation.

[c] Live births only.

Abbreviations: standard deviation (SD); Body mass index (BMI); University of California, San Francisco (UCSF), University of Minnesota (UMN), University of Rochester Medical Center (URMC), University of Washington (UW).

Table 2.

Geometric Mean (95% CI) of specific gravity-corrected urinary oxidative stress biomarkers (ng/mL) by timing of delivery

	Overall population (n=740)	Term birth (n=679)	Preterm birth (n=61)	p-value
Measured				
8-iso-$PGF_{2\alpha}$	0.95 (0.91, 0.99)	0.95 (0.91, 0.99)	0.97 (0.81, 1.16)	0.84
8-iso-$PGF_{2\alpha}$ metabolite	0.64 (0.62, 0.67)	0.64 (0.62, 0.66)	0.75 (0.67, 0.84)	0.01
$PGF_{2\alpha}$	2.05 (1.94, 2.17)	2.06 (1.94, 2.18)	2.02 (1.66, 2.46)	0.85
Derived				
8-iso-$PGF_{2\alpha,}$ enzymatic	0.16 (0.14, 0.18)	0.16 (0.14, 0.18)	0.14 (0.08, 0.24)	0.56
8-iso-$PGF_{2\alpha,}$ chemical	0.58 (0.65, 0.61)	0.57 (0.54, 0.61)	0.58 (0.44, 0.76)	0.91

Table 3.

Adjusted[a] odds ratios (95% confidence interval) for 1) preterm birth or 2) spontaneous preterm birth[b] with an interquartile range increase in specific gravity corrected urinary oxidative stress biomarker

	Association with preterm birth (n=624 term, 57 preterm)[c]	p-value	Association with spontaneous preterm birth (n=624 term, 39 preterm)	p-value
8-iso-$PGF_{2\alpha}$	0.93 (0.65, 1.32)	0.67	0.97 (0.63, 1.49)	0.89
8-iso-$PGF_{2\alpha}$ metabolite	1.44 (1.00, 2.06)	0.05	1.45 (0.96, 2.20)	0.08
$PGF_{2\alpha}$	0.86 (0.61, 1.22)	0.40	0.94 (0.62, 1.42)	0.77

a. Adjusted for race (white, black, other), maternal age (continuous), pre-pregnancy BMI (continuous), specific gravity, and gestational age at sample collection.

b. Spontaneous preterm birth is defined as preterm birth following PPROM or spontaneous labor.

c. 59 women (4 preterm, 55 term) were excluded due to missing covariate information.

Table 4.

Adjusted[a] accelerated time to 1) any or 2) spontaneous delivery (percent change with 95% confidence interval) in association with an interquartile range increase in specific gravity corrected urinary oxidative stress biomarker (n=681)[b]

	Any delivery	Spontaneous delivery[c] n_{cases}=394
8-iso-$PGF_{2\alpha}$	−0.09 (−0.40, 0.22)	−0.02 (−0.47, 0.43)
8-iso-$PGF_{2\alpha}$ metabolite	−0.19 (−0.50, 0.12)	−0.11 (−0.56, 0.34)
$PGF_{2\alpha}$	0.14 (−0.13, 0.41)	0.06 (y0.33, 0.45)

[a] Adjusted for race (white, black, other), maternal age (continuous), pre-pregnancy BMI (continuous), specific gravity, and gestational age at sample collection.

[b] 59 women (29 with spontaneous delivery) were excluded due to missing covariate information

[c] Spontaneous labor or PROM leading to delivery