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Extending Nontargeted Discovery of Environmental Chemical Exposures during Pregnancy and Their Association with Pregnancy Complications—A Cross-Sectional Study

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Background: Nontargeted analysis (NTA) methods identify novel exposures; however, few chemicals have been quantified and interrogated with pregnancy complications.

Objectives: We characterized levels of nine exogenous and endogenous chemicals in maternal and cord blood identified, selected, and confirmed in prior NTA steps, including linear and branched isomers perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS), monoethylhexyl phthalate, 4-nitrophenol, tetraethylene glycol, tridecanedioic acid, octadecanedioic acid, and deoxycholic acid. We evaluated relationships between maternal and cord levels and between gestational diabetes mellitus (GDM) and hypertensive disorders of pregnancy in a diverse pregnancy cohort in San Francisco.

Methods: We collected matched maternal and cord serum samples at delivery from 302 pregnant study participants from the Chemicals in Our Bodies cohort in San Francisco. Chemicals were identified via NTA and quantified using targeted approaches. We calculated distributions and Spearman correlation coefficients testing the relationship of chemicals within and between the maternal and cord blood matrices. We used adjusted logistic regression to calculate the odds of GDM and hypertensive disorders of pregnancy associated with an interquartile range increase in maternal chemical exposures.

Results: We detected linear PFOS, PFHxS, octadecanedioic acid, and deoxycholic acid in at least 97% of maternal samples. Correlations ranged between −0.1 and 0.9. We observed strong correlations between cord and maternal levels of PFHxS, linear PFOS, and branched PFOS (coefficient = 0.9, 0.8, and 0.8, respectively). An interquartile range increase in linear and branched PFOS, tridecanedioic acid, octadecanedioic acid, and deoxycholic acid was associated with increased odds ratio (OR) of GDM [OR = 1.33 (95% CI: 0.89, 2.01), 1.24 (95% CI: 0.86, 1.80), 1.26 (95% CI: 0.93, 1.73), 1.24 (95% CI: 0.86, 1.80), and 1.23 (95% CI: 0.87, 1.75), respectively]. Tridecanedioic acid was positively associated with hypertensive disorders of pregnancy [OR = 1.28 (95% CI: 0.90, 1.86)].

Discussion: We identified both exogenous and endogenous chemicals seldom quantified in pregnant study participants that were also related to pregnancy complications and demonstrated the utility of NTA to identify chemical exposures of concern. https://doi.org/10.1289/EHP11546

Introduction

Prenatal exposures to environmental chemicals are ubiquitous in the United States[1,2] and studies have demonstrated they can have lifelong consequences for maternal and child health outcomes, such as cardiovascular disease, diabetes, and adverse neurodevelopment and reproductive outcomes.[3] However, fewer than 1% of >40,000 chemicals processed, imported, or used in the United States are regularly biomonitored,[4] and fewer still have been assessed for adverse health outcomes during pregnancy. Nontargeted analysis (NTA) coupled with a prioritization step, followed by quantification using targeted methods, can facilitate the identification and quantitation of previously unmeasured chemical exposures.[5] In addition, by identifying and measuring novel chemical exposures, we can investigate their relationship with pregnancy complications, identifying additional opportunities for prevention.

Increasingly, studies are applying NTA to better characterize exposure to toxic environmental chemicals seldom measured in pregnant study participants.[6,7] NTA studies in pregnant and nonpregnant populations have identified both known and novel chemical exposures, including per- and polyfluoroalkyl substances (PFAS), pesticides, flame retardants, and other industrial chemicals that have been linked with pregnancy complications.[7,8] For example, exposure to PFAS has been linked with increased risk of miscarriage and preeclampsia.[9] Likewise, chemicals with fatty acid–like structures, including PFAS and other long-chain hydrocarbons, can interact with abnormal fatty acid metabolism impacting placental development. The interaction between PFAS and fatty acid metabolism may contribute to pregnancy complications and adverse birth outcomes.[7,10,11,12] Other NTA studies have linked novel chemical exposures and metabolism biomarkers.[7,13] However, the vast majority of novel chemicals identified through NTA have not been evaluated for associations with pregnancy-related complications.

This study builds on previous NTA work done on the Chemicals in Our Bodies-2 (CIOB2) cohort, in which we detected >30,000 chemical features using high-resolution mass spectrometry (HRMS) and confirmed the molecular structures using analytical standards.[6,7,14] The aim of the present study was to describe the quantification of a subset of chemicals identified and prioritized through this prior NTA work, to explore the correlation between levels found in maternal serum and cord blood samples, and to evaluate the relationship between chemical levels in maternal serum and pregnancy complications.

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Methods

Data and Sample Collection

We enrolled pregnant participants in the CIOB2 cohort between 2014 and 2018 from the prenatal clinics at the Zuckerberg San Francisco General Hospital (SFGH) and Mission Bay/Moffit Long (MB/ML) hospitals. Participant recruitment and sample collection has been described elsewhere.[5,6,7,15] Briefly, participants were recruited during the second trimester of pregnancy, with eligibility criteria including being 18–40 years of age, English or Spanish speaking, with singleton pregnancies, and no diagnosed pregnancy complications at recruitment ($n = 635$). Pregnancy complications that would result in exclusion from our study included nonsingleton pregnancies, pregestational diabetes (type 1 or type 2), preeclampsia at enrollment in the current pregnancy, human immunodeficiency virus, and known fetal anomalies. Paired maternal and umbilical cord blood were collected from participants who agreed to bank their samples and be contacted for participation in future studies. A total of 324 participants had maternal–cord samples collected at delivery. Because of budget limitations, we selected 302 matched maternal–cord pairs for targeted semiquantitation of environmental chemicals for inclusion in the analysis. We included all maternal–cord pairs collected from SFGH ($n = 88$) and randomly selected from matched maternal and cord pairs from MB/ML hospitals to complete our analysis set (Figure S1). Maternal samples were collected at delivery, and cord blood was collected after delivery but before clamping whenever possible. Maternal and cord blood was collected in BD Vacutainer Plus serum tubes, spun at 3,000 rpm to collect the serum, and stored at −80°C until analysis. Study protocols were approved by the institutional review boards at the University of California, San Francisco and Berkeley (#13-12160).

Demographic information was collected via interviews conducted during the second trimester of pregnancy and included maternal age, and race and ethnicity [White, Latinx, and non-Hispanic Asian/Pacific Islander, other race (owing to low numbers of Black, Native American, and multiracial participants, these groups were collapsed into "other" for model specification)], maternal education (some college or less, completed a college degree, graduate degree or higher), household income (<$40,000, $40,000–$100,000, >$100,000/y), nativity (born in the United States; yes or no). We abstracted the following data from the medical record data: prepregnancy body mass index (BMI; <18.5, 18.5 to <25, 25 to <35, ≥35 kg/m^2)[16] insurance type (public, private, other), and hospital of delivery (SFGH or MB/ML). MB/ML hospitals are two hospitals in the University of California, San Francisco (UCSF) health care system and primarily serve patients with private health insurance, and their data were combined for this analysis.

Pregnancy complication outcomes were identified by clinical diagnoses and abstracted from the medical record data. These included the binary outcomes of gestational diabetes mellitus (GDM), at risk for GDM, preeclampsia, and pregnancy-related hypertension. In addition to identifying participants with a clinical diagnosis of GDM, we also confirmed the diagnosis using the results from pregnancy glucose tolerance tests. We defined individuals to be at risk for GDM if they failed at least one glucose test during the index pregnancy even if the participant passed subsequent tests and was not diagnosed with GDM. We combined GDM and at risk for GDM into one outcome because exposure to environmental chemicals can have more subtle effects beyond discrete clinical diagnosis of GDM. Similarly, we combined preeclampsia and pregnancy-related hypertension into one outcome labeled as hypertensive disorder of pregnancy because they make up part of a larger spectrum of pregnancy complications related to hypertension and they are biologically related.[17–19]

Chemical Selection

Nine environmental chemicals were measured in maternal and cord serum samples using semiquantitation approaches, as described below. Linear and branched isomers of perfluorooctane sulfonate (PFOS); perfluorohexane sulfonate (PFHxS); monoethylhexyl phthalate (MEHP), a metabolite of diethylhexyl phthalate, a common plasticizer;[20] 4-nitrophenol, a known endocrine disruptor used in pesticides, dyes, and pharmaceuticals;[21] tetraethylene glycol, a plasticizer and solvent used in metal lubricants, printing inks, and cosmetics;[22] tridecanedioic acid and octadecanedioic acid, abnormal fatty acids that have exogenous sources primarily from plastics synthesis;[23–25] and deoxycholic acid, a bile acid that is associated with GDM (Table 1).[30]

The selection and confirmation procedures of these chemicals has been described elsewhere.[6,7,14] Briefly, in previous NTA studies, 30 matched maternal and cord samples were scanned using HRMS in positive and negative ionization modes, identifying suspect chemicals called features. Detected features were matched to an in-house database, and the features were then prioritized for MS/MS fragmentation based on the ubiquity of exposure, feature intensity differences across demographic variables, and correlation between maternal and cord samples. Features were annotated according to the Schymanski criteria.[31] Level 5 is assigned to those features with only the exact mass and for which we have the least certainty of their true identity. Level 1 features are chemicals that have a confirmed identity via comparison with an analytical standard.[31] Fifteen chemicals were confirmed at level 1 confidence and included monoethylhexyl phthalate, 4-nitrophenol, tridecanedioic acid, and octadecanedioic acid. Subsequent generalized suspect screening analysis of this cohort was expanded to include 295 matched maternal and cord samples and a more comprehensive database that included both endogenous and exogenous compounds. This resulted in 19 chemicals confirmed with analytical standards to level 1 confidence, including those previously identified to level 1, and added PFHxS, PFOS, and deoxycholic acid, which were tentatively identified through MS/MS fragmentation to confidence level 2—that is, that the chemicals contain a probable structure identified through empirical evidence and chemical fragmentation data from analytical methods.[14] We selected chemicals for semiquantitation if the chemical had been identified in a previous NTA with level 1 or level 2 confidence, was a widely used industrial compound with high potential for exposure, was associated with pregnancy complications, or was not regularly biomonitored by the Centers for Disease Control and Prevention or in other large biomonitoring studies (Figure 1).[6]

Semiquantitation Analysis of Selected Chemicals

Quantitation analysis of the nine selected chemicals was carried out using the Agilent MassHunter Quantitative Analysis software package (version 10.0; Agilent Technologies Inc.). Analytical grade standards were purchased from Sigma Aldrich or Thermo Fisher, and serial dilutions of the standards were prepared in methanol. The calibration curve of each of the specific standard was acquired under the same condition as the serum sample analysis, using liquid chromatography/quadrupole time-of-flight–MS (LC/QTOF-MS) (Agilent 1290 ultra performance LC interfaced with the Agilent iFunnel 6550 QTOF-MS system), as described previously.[6,7,14] Perfluorooctanoate (M2-PFOA; Wellington Laboratories) was used as the internal standard for the negative ionization chemicals, whereas triphenyl phosphate-d15 (D15-TPP; Cambridge Isotope Laboratories) was used for the positive ionization chemicals. In particular, PFOS in serum samples was separated with linear chromatography, thus both total and linear PFOS quantitation were

Table 1. Chemical uses and sources of the nine chemicals identified from nontargeted analyses (NTAs) and selected for confirmation and quantification.

Name	Sources, uses, and other information	Approximate production volume[a]	Biomonitored in humans
Perfluoroalkyl substances (PFAS) including: branched perfluorooctane sulfonate (PFOS), linear PFOS, and perfluorohexane sulfonate (PFHxS)	Industrial chemicals used for stain, water, and fire resistance. Used in fabrics and food packaging.[26] PFAS are high production volume chemicals.	>453,592 kg/y (>1 million lb/y)	Yes
Deoxycholic acid	A naturally occurring bile acid that is added as an emulsifier in food.[27]	Unknown	No
Tridecanedioic acid	Abnormal fatty acid also used in plastic and resin manufacturing.[23,24]	<453,592 kg/y (<1 million lb/y)	No
Octadecanedioic acid	Abnormal fatty acid also used in plastic and resin manufacturing.[25]	11,789 kg (25,990 lb) in 2019	No
Monoethylhexyl phthalate (MEHP)	Secondary diethylhexyl phthalate (DEHP) metabolite. DEHP is a common plasticizer. DEHP is a high production volume chemical.	>453,592 kg/y (>1 million lb/y)	Yes
Tetraethylene glycol (TEG)	Industrial solvent used in cosmetics, fragrances, manufacturing, food contact, industrial fluids, lubricants.[28]	4,535–22,698 kg/y (10,000–50,000 lb/y)	No
4-Nitrophenol	Xenobiotic metabolite of the pesticides parathion and methyl parathion, 4-nitroanisole.[21,29]	Unknown	No

Note: EPA, Environmental Protection Agency.
[a]Approximate production volume taken from the Chemical Data Reporting (CDR), a U.S. EPA program where companies/manufacturers report quantities of chemicals being used and imported.

calculated and branched PFOS concentrations were obtained by subtracting the linear portion from the total PFOS.

Statistical Analysis

To address chemical levels below the limit of detection (LOD), we used machine-reported values when available or, if not available, we imputed levels below the LOD with the LOD divided by the square root of 2. We assessed the detection frequency (percentage above the LOD) and limited our statistical analysis to chemicals with a detection frequency of 65% or higher to limit the amount of uncertainty that can result from high levels of nondetects. We described the distribution of chemicals in maternal and cord blood samples, and calculated Spearman correlation coefficients for chemicals within and between maternal and cord samples. We used the values measured in the maternal samples to evaluate the relationship between maternal chemical exposures and pregnancy complication. We applied logistic regression models to natural log-transformed exposure variables. Potential confounders for our logistic regression models were identified *a priori*[32] (Figure S2), and our final models were adjusted for maternal age, hospital of delivery, and race/ethnicity and evaluated as a complete case analysis. We considered hospital of delivery as a cumulative indicator of socioeconomic status (including income, educational attainment, and insurance status). Patients in both hospitals are racially and ethnically diverse.[33] However, SFGH is a safety net hospital that serves a large proportion of patients without private health insurance, whereas MB/ML hospitals serve patients of higher socioeconomic status with private health insurance (Table S1).[33] Race and ethnicity were included in models as an indicator of the exposure to structural racism, which is independently associated with chemical exposure and adverse pregnancy complications. We calculated the interquartile range (IQR) of each chemical. Beta coefficients and 95% confidence intervals (CIs) were multiplied by the IQR and exponentiated to identify the odds ratio (OR) of each pregnancy complication for each IQR increase in exposure level.

Results

Participants, Demographics, and Medical Record Data

The analysis included 302 participants (Table 2). The average age at delivery was 33 y. Forty-three percent of participants identified as White and 32% as Latinx or Hispanic. Most participants

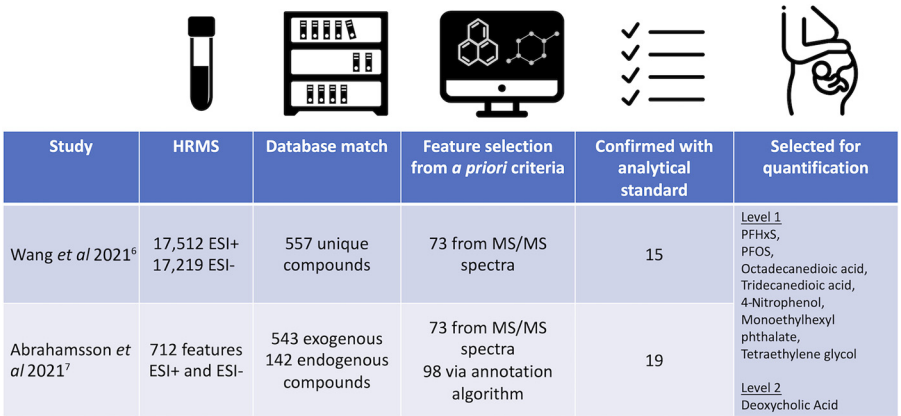

Figure 1. Summary of NTA procedures leading to the selection of nine chemicals for quantification with targeted approaches. Note: ESI, electrospray ionization; HRMS, high-resolution mass spectrometry; MS/MS, tandem mass spectrometry; NTA, nontargeted analysis; PFHxS, perfluorohexane sulfonate; PFOS, perfluorooctane sulfonate.

Table 2. Demographic variables and outcomes in Chemicals in Our Bodies-2 participants ($n = 302$) recruited between 2014 and 2018 in San Francisco, California.

	Mean ± SD or *n* (%)
Covariates	
Maternal age at delivery (y)	33 ± 5
Race/ethnicity	
White	130 (43)
Latinx	96 (32)
Asian	45 (15)
Other or Unknown[a]	31 (10)
Education	
Some college or less	97 (33)
College degree	73 (25)
Graduate degree	125 (42)
Missing	7
Household income per year	
<$40,000	68 (25)
$40,000–$100,000	37 (13)
>$100,000	170 (62)
Missing	27
Born in United States	
No	139 (47)
Yes	159 (53)
Missing	4
Prepregnancy BMI (kg/m^2)[b]	
<18.5	6 (2)
18.5 to <25	147 (55)
25 to <30	73 (27)
≥30	41 (15)
Missing	35
Hospital of Delivery	
San Francisco General Hospital	88 (29)
Mission Bay or Moffit Long	213 (71)
Missing	1
Insurance Type	
Private	178 (66)
Public	85 (31)
Other[c]	7 (3)
Missing	32
Outcomes	
GDM and at risk for GDM[d]	
No	223 (81)
Yes	57 (19)
Missing	2
At risk for GDM	20 (7)
Preeclampsia	
No	268 (93)
Yes	20 (7)
Missing	14
Gestational hypertension	
No	248 (86)
Yes	39 (14)
Missing	15
Hypertensive disorders of pregnancy[e]	
None	238 (83)
Any	50 (17)
Missing	14

Note: BMI, body mass index; GDM, gestational diabetes mellitus; SD, standard deviation.
[a]Race and ethnicity categories were collapsed for use in logistic regression models owing to small numbers in some categories. Other/unknown includes Black, Native Hawaiian or Pacific Islander, Native American, multiracial, and individuals of unknown race.
[b]BMI is calculated as kilograms per meter squared and cutoffs are based on the Centers for Disease Control and Prevention guidelines.[16]
[c]"Other" insurance includes Covered California or other insurance from the San Francisco health care system that could be either public or private.
[d]Includes diagnosis of GDM and at risk for GDM. At risk for GDM means they did not have a clinical diagnosis but failed at least one glucose tolerance test during the index pregnancy.
[e]Combines preeclampsia and gestational hypertension, some participants are diagnosed with both, so the total number combined is less than the sum of each individual diagnosis.

completed college or graduate degrees (67%), were born in the United States (53%), and had a household income of >$100,000/y (62%). For the outcomes, 19% of participants had a diagnosis of GDM, 14% gestational hypertension, and 7% preeclampsia.

Distribution and Correlation of Chemical Levels in Maternal Samples

Participants had at least four chemicals in maternal samples and three chemicals in cord samples. PFHxS, linear PFOS, deoxycholic acid, and octadecanedioic acid were all detected in at least 97% of maternal samples. Deoxycholic acid, tridecanedioic acid, and PFHxS were detected in at least 87% of cord blood samples (Table 3). Given that we estimated branched PFOS levels by subtracting linear PFOS from the total PFOS, we did not calculate a detection frequency for this chemical. Chemical detection frequency varied between maternal and cord blood samples. Linear PFOS, and 4-nitrophenol were detected more often in maternal samples, whereas monoethylhexyl phthalate, and tridecanedioic acid were detected more frequently in cord blood. Average chemical levels also varied across the different matrices—the level of branched PFOS was 33% higher, linear PFOS was 45% higher, and deoxycholic acid and octadecanedioic acid were both 77% higher in maternal serum than in cord samples, whereas tridecanedioic acid was 31% higher in cord than in maternal samples.

Monoethylhexyl phthalate, tetraethylene glycol, and 4-nitrophenol were each detected in fewer than 50% of maternal samples; however, 4-nitrophenol was detected in more maternal serum samples than cord samples, whereas monoethylhexyl phthalate was found in more cord blood samples. Because of their low detection frequency, monoethylhexyl phthalate, tetraethylene glycol, and 4-nitrophenol were excluded from further analyses.

When assessing the Spearman correlation coefficients (Figure 2) of the same chemical across maternal and cord samples, we found that linear PFOS, and branched PFOS and PFHxS were highly correlated in the maternal and cord samples (correlation coefficients of 0.8, 0.8, and 0.9 respectively). When looking at the correlations of different chemicals in the maternal and cord samples, we found moderate correlations between cord–linear PFOS and maternal–branched PFOS, as well as between cord–linear PFOS and maternal–PFHxS (coefficients 0.7 and 0.5, respectively). In the cord blood samples, linear PFOS was highly correlated with branched PFOS and moderately correlated with PFHxS (coefficients of 0.8 and 0.6, respectively), and octadecanedioic acid was moderately correlated with tridecanedioic acid (coefficient of 0.4). In the maternal samples, the relationship between linear and branched PFOS had a correlation coefficient of 0.8, branched PFOS and PFHxS a correlation of 0.6, and linear PFOS and PFHxS a correlation of 0.6. The PFAS chemicals were weakly correlated with the fatty acids octadecanedioic acid and tridecanedioic acid and neither PFAS nor the fatty acids were correlated with deoxycholic acid, within or between the maternal serum and cord blood samples.

Association between Chemical Exposure with Pregnancy Complications

From our logistic regression models, we observed a trend of increased odds of GDM for each IQR increase in levels of exposure to environmental chemicals and increased odds of pregnancy hypertensive disorders with tridecanedioic acid (Table 4). Stronger associations were observed for branched PFOS, linear PFOS, octadecanedioic acid, tridecanedioic acid, and deoxycholic acid; the direction and measures of association we observed between chemical levels and hypertensive disorders of pregnancy was less consistent than for GDM. Exposure to tridecanedioic acid was associated with an increase in the odds of hypertensive disorders of pregnancy [OR = 1.28 (95% CI: 0.90, 1.86)]. Exposure to tridecanedioic acid was also associated in

Table 3. Distribution of chemical levels (ng/mL) in maternal serum ($n = 302$) and cord blood ($n = 299$).

Chemical	Sample	LOD	DF (%)	GM	GSD	Min	Max	Percentile			
								25	50	75	95
Branched PFOS (ratio GM maternal/cord: 1.5)[a]											
	Cord	NR	NR	0.2	2.4	0	1.3	0.1	0.2	0.3	0.6
	Maternal	NR	NR	0.3	2	0	3	0.2	0.3	0.5	1
Linear PFOS (ratio GM maternal/cord: 1.8)											
	Cord	0.43	67	0.6	1.6	<LOD	3.8	<LOD	0.5	0.8	1.4
	Maternal	0.43	97	1.1	1.8	<LOD	6.7	0.7	1	1.6	3.1
PFHxS (ratio GM maternal/cord: 1.3)											
	Cord	0.11	98	0.3	1.6	<LOD	2.6	0.2	0.3	0.4	0.7
	Maternal	0.11	100	0.4	1.8	<LOD	4.2	0.3	0.4	0.5	1.1
Tridecanedioic acid (ratio GM maternal/cord: 0.7)											
	Cord	6.79	86	11.2	1.6	<LOD	47.7	8.1	11.2	14.9	23.7
	Maternal	6.79	67	7.7	1.5	<LOD	26.2	6.3	8.1	9.9	14
Octadecanedioic acid (ratio GM maternal/cord: 4.4)											
	Cord	0.48	100	3.1	1.8	0.5	35.7	2.2	3	4.3	9.2
	Maternal	0.48	100	13.6	2	1.9	102.8	8.6	13.6	21.8	40.3
Deoxycholic acid (ratio GM maternal/cord: 4.4)											
	Cord	0.81	99	3.7	2.2	<LOD	54.4	2.2	3.2	5.7	15.3
	Maternal	0.81	99	16.1	3.4	<LOD	432.6	7.5	16.5	37.1	104.8
Monoethylhexyl phthalate (ratio GM maternal/cord: NA)											
	Cord	5.19	58	6.7	2.7	<LOD	136.1	<LOD	6	10.7	50.4
	Maternal	5.19	44	<LOD	<LOD	<LOD	452.6	<LOD	<LOD	16	60.2
Tetraethylene glycol (ratio GM maternal/cord: 1.0)											
	Cord	2.1	43	3	3.1	<LOD	358	<LOD	<LOD	4.7	35.3
	Maternal	2.1	43	2.9	2.9	<LOD	226.2	<LOD	<LOD	5	24.3
4-Nitrophenol (ratio GM maternal/cord: NA)											
	Cord	0.67	17	<LOD	1.5	<LOD	1.6	<LOD	<LOD	<LOD	0.9
	Maternal	0.67	27	<LOD	1.6	<LOD	2.5	<LOD	<LOD	0.7	1

Note: The sample size is smaller for cord blood samples because we were not able to collect cord blood from a small number of participants. DF, detection frequency; GM, geometric mean; GSD, geometric standard deviation; LOD, limit of detection; Max, maximum; Min, minimum; NA, not applicable; NR, not reportable; PFHxS, perfluorohexane sulfonate; PFOS, perfluorooctane sulfonate.

[a]The LOD and DF for branched PFOS were not reportable because they were estimated by subtracting the levels of linear PFOS from the total PFOS. Maternal/cord ratio illustrates transfer efficiency between maternal and cord matrices and was calculated by GM(Maternal)/GM(Cord). Summary statistics were calculated for each analyte in the full sample for cord and maternal serum.

increased odds of the separate outcomes of preeclampsia and gestational hypertension (Table S2). The ORs for PFHxS, octadecanedioic acid, and deoxycholic acid with gestational hypertension approximated the null, and linear and branched PFOS had an OR of <1.

Discussion

Building on NTA steps from prior studies,[6,7,14] we confirmed and quantified the presence of nine chemicals. To our knowledge, tridecanedioic acid, octadecanedioic acid, and tetraethylene glycol have not been previously measured in pregnant study participants,

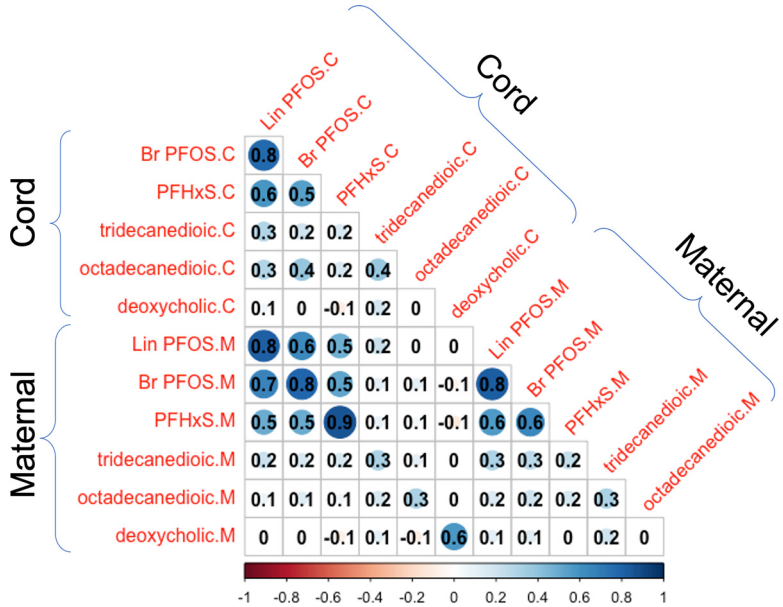

Figure 2. Spearman correlation coefficients for chemicals detected in maternal and cord serum samples, chemicals have at least 65% DF (maternal $n = 302$, cord $n = 299$). Chemical names ending in ".M" refer to maternal samples, and ".C" to cord blood samples. Note: Br, branched; DF, detection frequency; Lin, linear; PFHxS, perfluorohexane sulfonate; PFOS, perfluorooctane sulfonate.

Table 4. Adjusted and unadjusted ORs and 95% CIs from logistic regression models of the relationship between an interquartile range (IQR) chemical exposure in maternal serum at delivery and pregnancy complications ($n = 302$).

Chemical	Model	OR (95% CI) Gestational diabetes[a]	OR (95% CI) Hypertensive disorders[a]
Number missing		0	14
N (%) with outcome		77 (25)	50 (17)
Branched PFOS (IQR: 1.01)			
	Unadjusted	1.32 (0.91, 1.92)	1.05 (0.68, 1.62)
	Adjusted	1.33 (0.89, 2.01)	1.06 (0.65, 1.71)
Linear PFOS (IQR: 0.76)			
	Unadjusted	1.30 (0.93, 1.83)	0.85 (0.56, 1.27)
	Adjusted	1.24 (0.86, 1.80)	0.89 (0.56, 1.39)
PFHxS (IQR: 0.59)			
	Unadjusted	1.09 (0.83, 1.41)	1.00 (0.72, 1.35)
	Adjusted	1.10 (0.82, 1.46)	0.98 (0.67, 1.38)
Octadecanedioic acid (IQR: 0.93)			
	Unadjusted	1.19 (0.84, 1.70)	1.05 (0.69, 1.63)
	Adjusted	1.24 (0.86, 1.80)	1.00 (0.65, 1.54)
Tridecanedioic acid (IQR: 0.46)			
	Unadjusted	1.31 (0.97, 1.79)	1.25 (0.88, 1.80)
	Adjusted	1.26 (0.93, 1.73)	1.28 (0.90, 1.86)
Deoxycholic acid (IQR: 1.60)			
	Unadjusted	1.25 (0.89, 1.78)	0.96 (0.65, 1.43)
	Adjusted	1.23 (0.87, 1.75)	0.97 (0.65, 1.45)

Note: Adjusted model includes the covariates of maternal age, hospital of delivery, and race/ethnicity. CI, confidence interval; GDM, gestational diabetes mellitus; OR, odds ratio; PFHxS, perfluorohexane sulfonate; PFOS, perfluorooctane sulfonate.
[a]Includes both GDM and at risk for GDM.
[b]Includes both preeclampsia and gestational hypertension.

whereas deoxycholic acid and 4-nitrophenol have rarely been measured in pregnant study participants. We found an association between chemical exposure levels and GDM, as well as between chemical exposure and hypertensive disorders of pregnancy. Linear and branched PFOS exposure was associated with increased odds of GDM and tridecanedioic acid exposure was associated with hypertensive disorders of pregnancy. This study adds to our understanding of the relationship between environmental exposures during pregnancy and pregnancy complications.

This study provides further evidence of prenatal exposure to environmental chemicals, some of which have positive associations with pregnancy complications. A 2020 study suggested that PFAS exposure during pregnancy may also affect metabolic pathways that adversely impact placental development.[10] Although the evidence remains mixed, exposure to PFAS has been shown to be associated with hypertensive disorders of pregnancy, preeclampsia, and GDM.[10,34,35,36] The linear and branched forms of PFOS have not previously been well characterized during pregnancy. Furthermore, metabolism, excretion, and placental transfer may vary by the linear and branched forms of this ubiquitous chemical and lead to different health outcomes and pregnancy complications.[26]

We found evidence that the linear and branched forms of PFOS may have a relationship with pregnancy complications. Branched and linear PFOS were significantly associated with GDM in unadjusted models, and although the relationship was attenuated in adjusted models, the direction and magnitude of the association were maintained. Indeed, traditional PFOS production yielded a mixture of branched and linear isomers with $\sim 30\%$ of isomers in the branched form.[26] Scientific evidence supports the transplacental transfer of PFAS chemicals.[7,37,38] In addition, GDM may facilitate transplacental transfer of PFOS given that GDM is associated with alterations to the kinetic disposition of environmental chemicals and placental capillarization influencing the rate of transplacental transfer.[39] Linear PFOS, which makes up a larger proportion of the measured PFOS,[26] is hypothesized to remain longer in maternal serum and therefore more available in maternal samples than branched PFOS. Animal and human studies have shown that linear PFOS may adsorb more strongly to serum proteins making it less able to cross the placenta and less available for renal clearance, which may contribute to the differences in association we observed with GDM.[40,41] We observed a higher proportion of patients with GDM in our study (19%) compared with national averages (1%–10%)[42] or the averages reported for California (10% in 2014).[43] The larger proportion of GDM observed in our study participants may, in part, be explained by the demographics of our study population given that women of color have higher rates of GDM that is only partially explained by prepregnancy BMI and other factors.[44,45] Maternal age is another factor for increased risk of GDM and glucose intolerance[46] and MB/ML hospitals serve high-risk pregnancies, including an older maternal population. Drinking water is an important source of PFAS exposure in many communities; however, in San Francisco and the surrounding areas, PFAS has not been detected in drinking water sources.[47,48] Therefore, in our study participants, PFAS exposure is likely to occur from food, food packaging, and other consumer products.[49] In addition, the significant positive correlations between branched PFOS, linear PFOS, and PFHxS in the maternal and cord samples suggest that they may share a common source of exposure. The levels of PFOS (linear and branched combined) and PFHxS measured in this study were lower than those reported for reproductive-aged women in the National Health and Nutritional Examination Survey (NHANES) during a similar time frame,[15] but the levels were consistent with the PFOS and PFHxS levels previously measured in the San Francisco cohort.[15,50]

Previous studies have found that increased exposure to fatty acids may be associated with an increased risk of hypertensive disorders of pregnancy due to disruption of fatty acid regulation and metabolism.[51] The sources of the fatty acids tridecanedioic acid and octadecanedioic acid are not well known, although they are included in the Toxic Substances Control Act (TSCA) inventory of chemicals produced in the United States.[52] We observed an association between tridecanedioic acid and hypertensive disorders of pregnancy, but not for octadecanedioic acid. The abnormal fatty acid chemicals in our study are used in plastics production and have seldom been studied in pregnant women.[14]

Tetraethylene glycol, 4-nitrophenol, and monoethylhexyl phthalate were not evaluated for associations with pregnancy complications because their detection frequency in maternal samples was $<65\%$. These chemicals have short half-lives in serum (<24 h), they are quickly metabolized and excreted from the body via urine, contributing to their low detection frequency in serum samples, which could be a factor in our inability to detect these compounds in blood.[21,53,54] Our study demonstrates that novel exposures to these environmental chemicals can still be identified through nontargeted methods and confirmed through targeted approaches in blood. These are high production volume chemicals that may interact with endocrine disruption and metabolic pathways. In addition, the relationship of tetraethylene glycol and 4-nitrophenol with adverse reproductive or pregnancy outcomes has not been previously assessed and warrants further study, including evaluating whether urine is a better matrix for detecting exposures.

There are several limitations that may influence the associations we observed in our study. First is the timing of the collection of samples and assessment of health outcomes. This was a cross-sectional study with both maternal and cord blood samples collected at delivery, and pregnancy complications were identified from clinical diagnosis during the pregnancy and were abstracted from medical record data. Because of the timing of our sample collections at delivery, the assessment of the outcome came before the measurement of chemicals, precluding our being

able to assess causality in the present study. Nevertheless, the chemicals included in this study are industrial chemicals, many of which are high production volume chemicals to which participants are constantly exposed. For example, PFAS chemicals are ubiquitous in biological matrices and the environment, and tridecanedioic acid and octadecanedioic acid are used in the synthesis of plastics and are considered high production volume chemicals.[23] The chemical measurements reflect a snapshot of an individual's exposure history during pregnancy; however, the sources and uses of these environmental chemicals imply that there is a potential for prolonged exposure throughout the pregnancy. In addition, studies have demonstrated consistency of PFAS levels from the first through the third trimesters.[55] Another potential limitation is that levels of branched PFOS were estimated from the analytical standard from the linear isomer and not quantified with its own analytical standard, reducing the precision of the calculated measures of association. For other chemicals with values below the LOD, we used machine-reported values when available, substituting the LOD with the LOD divided by square root of 2, which may not fully represent the distribution of chemical levels below the LOD and possibly lead to biased or unprecise estimates. The low detection frequency of 4-nitrophenol, tetraethylene glycol, and monoethylhexyl phthalate precluded our ability to assess the chemical–outcome relationship. However, these chemicals remain understudied in pregnant study participants and are of high concern owing to their widespread use as industrial chemicals and limited understanding of their health effects. Our modest study sample size precluded our ability to examine stratified results by race/ethnicity (as proxy coexposures related to structural racism) that could amplify observed relationships between chemical exposures and risk of GDM. Finally, given the timing of recruitment in the second trimester, and that individuals with pregnancy complications in the index pregnancy were excluded, we may have missed early manifestations of pregnancy complications if they occurred before the time of recruitment at the second trimester visit. However, diagnosis of hypertensive disorders of pregnancy and testing for GDM usually occurs after 24 wk of pregnancy, whereas our participants were recruited earlier in the second trimester.[56,57]

In this analysis we identified and quantified exogenous and endogenous environmental chemicals, some of which have not been previously measured during pregnancy or evaluated for associations with pregnancy complications. Our study supports prior reports of associations between the branched and linear forms of PFOS and GDM and adds to the limited research on exposure to tridecanedioic acid and octadecanedioic acid—both endogenous fatty acids that also have industrial sources. Finally, this study further illustrates the benefit of pairing nontargeted and targeted approaches to identify, confirm, and quantify novel chemical exposures. Supplementing the nontargeted discovery of chemicals with targeted semiquantitation addresses some of the limitations of NTA; that is, targeted approaches increase sensitivity, allowing us to compare chemical concentrations and assess the relationship between chemicals and pregnancy complications. Combining NTA methods with targeted chemicals measurement can be further applied to identifying, quantifying, and evaluating metabolism biomarkers that are on the pathway between exposure and downstream adverse health effects.

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