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Are perfluorooctane sulfonate alternatives safer? New insights from a birth cohort study

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ABSTRACT

Background: Experimental studies show that chlorinated polyfluorinated ether sulfonic acids (Cl-PFESA 6:2 and 8:2), one of perfluoroalkyl substances (PFAS) used as perfluorooctane sulfonate (PFOS) alternatives, are reproductive toxicants *in vivo* and *in vitro*. However, the associations between gestational exposure to Cl-PFESAs and birth outcomes are unknown.

Objectives: We investigated associations between 6:2 Cl-PFESA and 8:2 Cl-PFESA in maternal serum and birth outcomes.

Methods: We measured four PFAS, including 6:2 Cl-PFESA, 8:2 Cl-PFESA, PFOS, and perfluorooctanoic acid (PFOA) in third-trimester maternal serum collected from 372 mother-child dyads participating in the Guangzhou Birth Cohort Study. Characteristics of mothers and infants were gathered from medical records and by interviewer-administered questionnaires.

Results: PFOS was the most abundant PFAS in maternal serum (median: 7.15 ng/mL), followed by 6:2 Cl-PFESA (median: 2.41 ng/mL). Greater maternal serum levels of all PFAS alternatives were significantly associated with lower birth weight, adjusted for confounding variables. For example, each ln-ng/mL greater concentration of 6:2 Cl-PFESA and 8:2 Cl-PFESA was associated with a 54.44 g [95% confidence interval (CI): −95.66, −13.22] and 21.15 g (95% CI: −41.44, −0.86) lower birth weight, respectively. Greater continuous maternal serum 6:2 Cl-PFESA (OR: 2.67, 95% CI: 1.73, 4.15) and PFOS (OR: 2.03, 95% CI: 1.24, 3.32) were also associated with higher risks for preterm birth, adjusted for confounders, with a possible threshold effect at the highest quartile of 6:2 Cl-PFESA.

Conclusions: For the first time, we report associations between maternal serum 6:2 Cl-PFESA and 8:2 Cl-PFESA concentrations and adverse birth outcomes. Our findings suggest that PFOS alternatives may be reproductive toxicants in human populations and should be considered with caution before widespread use. Given the preliminary nature of our results, additional epidemiological and toxicological investigations are needed to more definitively assess the risks.

1. Introduction

Poly- and perfluoroalkyl substances (PFAS) have been used in myriad industrial and commercial products, and have been recognized as environmental pollutants due to their persistence, toxicity and bioaccumulative properties (Sunderland et al., 2019). Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) have been used most extensively and are the most widely studied PFAS to date (Negri et al., 2017). However, production of PFOS and PFOA, which are listed as persistent organic pollutants by the Stockholm Convention, has been

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phased out by many developed nations (U.S. Environmental Protection Agency, 2006). As a party to the Stockholm Convention, China also endeavors to reduce and eliminate PFOS and PFOA production (Liu et al., 2016).

Chlorinated polyfluorinated ether sulfonic acids (Cl-PFESAs), including 6:2 Cl-PFESA and 8:2 Cl-PFESA, have been introduced as PFOS alternatives. They are presumed to be less persistent due to the presence of an oxygen atom in the perfluoroalkyl chain (Figs. S1 and S2) (Wang et al., 2013). These agents, commercially named F-53B (CAS No. 73606-19-6), have been used primarily as mist suppressants for the electroplating industry in China since the 1970s (Wang et al., 2013, Wang et al., 2014, Wang et al., 2019). Near universal use led to widespread environmental contamination in China. Recent studies detected 6:2 Cl-PFESA and 8:2 Cl-PFESA in various environmental matrices (Ruan et al., 2015, Lin et al., 2016, Wang et al., 2016, Kato et al., 2018, Pan et al., 2018) and human biospecimens (Shi et al., 2016, Chen et al., 2017, Pan et al., 2017). Due to its persistence and long-range transport, 6:2 Cl-PFESA has even been detected in remote areas, including in marine mammals from Greenland (Gebbink et al., 2016), so the health risks of Cl-PFESAs are likely to be global. Similar to other PFAS, dietary intake is the main route of human exposure to Cl-PFESAs, including consumption of contaminated seafood and water (Cui et al., 2018a, Fromme et al., 2009). Of great concern, 6:2 Cl-PFESA and 8:2 Cl-PFESA appear to cross the placenta and enter the fetal compartment more readily than PFOS, suggesting a developmental risk for maternal Cl-PFESAs exposures (Pan et al., 2017).

Previous epidemiologic studies suggest that prenatal exposure to PFOS and PFOA may be associated with adverse birth outcomes, such as lower birth weight and smaller gestational age (Bach et al., 2015, Negri et al., 2017, Steenland et al., 2018). Neonates with low birth weight and preterm birth that reflect fetal growth restriction (Nardozza et al., 2017) are at greater risk of death (Saigal and Doyle, 2008, Crump et al., 2011), neurodevelopmental delays (Aylward, 2014), cardiovascular disorders (Pocobelli et al., 2016) and other adverse health effects throughout life (Blencowe et al., 2012). Our previous work indicated associations between greater cord blood PFOS and lower birth weight (Li et al., 2017). However, there are few data available to assess the developmental risks of maternal 6:2 Cl-PFESA and 8:2 Cl-PFESA exposure in human populations.

To begin to address this research gap, we conducted an exploratory investigation of associations between prenatal 6:2 Cl-PFESA and 8:2 Cl-PFESA exposure with fetal growth in the Guangzhou Birth Cohort Study. We hypothesized that greater prenatal 6:2 Cl-PFESA and 8:2 Cl-PFESA exposure would be associated with lower birth weight and shorter gestational age at delivery, and that greater prenatal 6:2 Cl-PFESA and 8:2 Cl-PFESA exposure would be associated with higher risks for low birth weight and preterm birth.

2. Methods

2.1. Study population

The Guangzhou Birth Cohort included mothers receiving prenatal care at a single hospital in Guangzhou (Guangdong Province, China) from July to October 2013. Participant enrollment and the study protocol were previously described in detail (Li et al., 2017). Briefly, pregnant women 18 to 45 years of age, without self-reported cancer or psychiatric illness, and with live, singleton births were eligible to participate. Of 411 eligible women invited, 372 (90.5%) provided a blood sample for PFAS analysis. Blood was collected within three days of delivery by selecting the routine clinical collection made after admission to the hospital and closest to the date of delivery. Blood serum was separated by centrifugation at 3500*g* within 3 h of collection and kept at −80 °C until analysis. Study staff interviewed participants about demographic information (including maternal age, occupation, education, and family income), reproductive history (including parity and history of pregnancy losses), and lifestyle factors (including smoking habits and alcohol consumption among others). We abstracted relevant clinical information from the prenatal and delivery records, including newborn sex, birth weight, gestational age at delivery, and parity. Each participant provided written informed consent prior to enrollment and the local Institutional Review Board (Sun Yat-Sen University Research Ethics Committee) approved the study protocol.

2.2. Birth outcomes

We abstracted continuous birth weight (g) and gestational age (weeks) data from the electronic medical record as recorded by the midwife or attending physician at the time of delivery. Gestational age was estimated by the obstetrician according to Naegele's rule, using each participant's self-reported last menstrual period (LMP). Preterm birth was defined as gestational age at delivery < 37 weeks, and low birth weight (LBW) was defined as birth weight < 2500 g (WHO, 1977).

2.3. PFAS measurements

We measured PFAS concentrations in maternal serum samples using a modified version of the method developed by Benskin et al (Benskin et al., 2012). PFAS abbreviations and nomenclature are shown in Table S1, and detail about the internal standards is provided in Table S2. Detailed analytic methods describing the standards and reagents, sample extraction, liquid chromatography-mass spectrometry, and quality control in the present study is provided in the Supplementary Material. Briefly, extractions were based on 0.2 mL serum and were performed by solid phase extraction. The PFAS were separated and quantified using an Agilent 1290 UPLC attached to an Agilent 6495B triple-quadrupole tandem mass spectrometer (Agilent Technologies, Palo Alto, CA, USA), equipped with an electrospray interface operating in negative ion mode. The *m/z* 351.0 and 451.0 transition were selected as the quantitative product ions for 6:2 Cl-PFESA and 8:2 Cl-PFESA, respectively. All PFAS standards were purchased from Wellington Laboratories (Guelph, ON, Canada). The limit of detection (LOD) for each PFAS was defined as the minimum detectable concentration with a signal-to-noise ratio of 3 (S/N = 3) (Table S3). PFAS concentrations below the LOD were imputed as LOD divided by the square root of 2 (Hornung and Laurence, 1990).

2.4. Statistical analysis

Distributions were characterized for demographic factors, lifestyle factors, clinical factors, and PFAS concentrations in maternal sera. Maternal serum PFAS concentrations were natural log transformed to achieve a normal distribution. Splines indicated mostly linear relations between PFAS exposure and birth outcome, with the exception of a possible non-linear association between 8:2 Cl-PFESA and gestational age, and a possible threshold effect between 6:2 Cl-PFESA and gestational age. Generalized additive models (GAMs) were used to estimate associations of PFAS as predictors with birth weight and gestational age as outcomes. Because sex-specific effects were reported by previous studies (Maisonet et al., 2012, Sagiv et al., 2018), we also assessed interactions between PFAS and infant sex using GAMs and stratified by infant sex for interpretation. Cross-product terms between PFAS and infant sex were entered into adjusted regression models to test for statistical significance. We used logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) for low birth weight and preterm birth as functions of maternal serum PFAS. PFAS levels were entered as both continuous variables and categorical quartiles. We operationalized 8:2 Cl-PFESA based on three categories (≤LOD, > LOD–75th %tile, > 75th %tile) as there were few detectable values. To estimate *P*-values for trend we modeled an ordinal variable as the median value assigned for each corresponding PFAS category. We also

conducted sensitivity analyses by excluding participants with gestational diabetes mellitus (GDM), hypertension in pregnancy, and anemia given high risks for adverse pregnancy outcomes in these groups (Metzger et al., 2010, Lee and Okam, 2011, Malik and Kumar, 2017).

We identified potential confounders in the literature as common predictors of PFAS exposure and birth outcomes or their antecedents (Greenland et al., 1999). This included sources of PFAS exposure and factors likely to impact the absorption and excretion of PFAS (Savitz, 2007), that may also affect birth outcomes, such as age, parity, body mass index (BMI), and socioeconomic characteristics (Tian et al., 2018, Mohammad et al., 2014). We incorporated these factors into directed acyclic graphs (DAGs) to identify minimally sufficient covariate sets to adjust for confounding without introducing bias (Figs. S3 and S4). We retained infant sex (male and female), maternal age (years, continuous), maternal occupation (blue collar and white collar), maternal education (< high school and ≥high school), family income (< 4000, 4000–7999 and ≥8000 Yuan/month), and parity (0 and > 0) as potential confounders in the regression models. While somewhat controversial (Schisterman et al., 2009, Wilcox et al., 2011, Bach et al., 2015), we also considered gestational age at delivery (weeks, continuous) as a confounder in birth weight models, based on cumulative gestational PFAS exposure and the strong association with birth weight. We defined statistical significance as a two-tailed *P*-value < 0.05. The statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

The distribution of demographic, clinical factors, and select maternal PFAS concentrations in 372 gravidas are presented in Table 1, stratified by infant sex. Mothers were 27 years of age on average, predominantly blue-collar workers, high school educated, and tended to have a household income lower than 4000 Yuan/month. No participants reported smoking cigarettes or drinking alcohol during the study pregnancy. Average birth weights were 3139 g for males and 3133 g for females, with an average gestational age of 38 weeks overall. Among newborns, 8.9% had low birth weight and 10.5% were preterm births. With the exception of gestational hypertension, which was more prevalent among mothers of female infants (P < 0.001), distributions of covariates were similar between the mothers of male and female infants. All PFAS were measured above the LODs, with the exception of 40.9% of 8:2 Cl-PFESA, and concentrations were similar between mothers of male and female infants (Table S3). PFOS (7.15 ng/mL) was the dominant PFAS in maternal serum, followed by 6:2 Cl-PFESA (2.41 ng/mL), and PFOA (1.54 ng/mL). Spearman correlation coefficients between PFAS ranged from 0.33 to 0.79 (Table S4).

Table 2 shows associations of selected natural log-transformed PFAS levels in maternal serum with birth weight and gestational age, adjusted for confounders. We detected statistically significant inverse associations between all maternal serum PFAS concentrations and birth weight. For example, each ln-ng/mL greater 6:2 Cl-PFESA concentration was associated with a 54.44 lower birth weight (95% CI: −95.66, −13.22). As shown by Fig. 1(A), women in the highest quartile of 6:2 Cl-PFESA quartile had a mean birth weight of 3018 g (95% CI: 2936, 3100) compared with 3201 g (95% CI: 3122, 3280) in the 3rd quartile of 6:2 Cl-PFESA (*P* < 0.05), indicating a possible threshold effect. Some PFAS also showed inverse associations with gestational age. Each 1n-ng/mL greater maternal serum 6:2 Cl-PFESA was associated with 0.39 weeks shorter gestational age (95% CI: −0.56, −0.22) and −0.32 weeks (95% CI: −0.53, −0.11) for PFOS. As shown in Fig. 1(B), women in the highest 6:2 Cl-PFESA quartile had mean gestational age at delivery of 37.9 weeks (95% CI: 37.6, 38.3) compared with 38.6 weeks (95% CI: 38.3, 39.0) in the 3rd quartile of 6:2 Cl-PFESA, again suggesting a possible threshold effect. The associations between 6:2 Cl-PFESA and birth outcomes became weaker, after excluding participants with preterm birth (n = 39). Furthermore, 6:2 Cl-PFESA was not associated with birth weight after adding PFOS and PFOA to the model, and the association for 8:2 Cl-PFESA became weaker, but the associations between Cl-PFESAs and gestational age remained similar (Table S5). There was no statistically significant interaction between

Table 1
Distribution of demographic, clinical, and lifestyle factors among women with singleton pregnancies, by infant sex.

Characteristic	Total (n = 372)	Male (n = 186)	Female (n = 186)	*P*
Maternal age (years)[a]	27.4 ± 5.1	27.4 ± 5.2	27.5 ± 5.1	0.839
Gestational age (weeks)[a]	38.6 ± 1.7	38.6 ± 1.7	38.7 ± 1.7	0.628
Infant birth weight (g)[a]	3131.1 ± 466.8	3138.5 ± 438.0	3132.8 ± 495.0	0.762
Low birth weight[b,c]	33 (8.9)	14 (7.5)	19 (10.2)	0.362
Preterm delivery[b,d]	39 (10.5)	21 (11.3)	18 (9.7)	0.612
Maternal occupation[b]				
Blue collar	303 (81.5)	151 (81.2)	152 (81.7)	0.894
White collar	69 (18.5)	35 (18.8)	34 (18.3)	
Maternal education[b]				
< High school	129 (34.7)	67 (36.0)	62 (33.3)	0.586
≥High school	243 (65.3)	119 (64.0)	124 (66.7)	
Family income[b]				
< 4000	229 (61.6)	115 (61.8)	114 (61.3)	0.984
4000–7999	106 (28.4)	53 (28.5)	53 (28.5)	
≥8000	37 (10.00)	18 (9.7)	19 (10.2)	
Primipara[b]	205 (55.1)	108 (58.1)	97 (52.1)	0.252
Gestational diabetes mellitus[b]	27 (7.3)	15 (8.1)	12 (6.4)	0.549
Hypertension in pregnancy[b]	33 (8.9)	6 (3.2)	27 (14.5)	< 0.001
Anemia[b]	113 (30.4)	61 (32.8)	52 (28.0)	0.310
PFAS (ng/mL) in maternal serum				
6:2 Cl-PFESA[e]	2.405 (1.219, 4.686)	2.623 (1.489, 5.440)	2.170 (1.108, 4.151)	0.615
8:2 Cl-PFESA[e]	0.001 (0.001, 0.039)	0.001 (0.001, 0.052)	0.001 (0.001, 0.037)	0.637
PFOS[e]	7.153 (4.361, 11.928)	7.652 (4.607, 11.672)	6.474 (3.956, 11.950)	0.972
PFOA[e]	1.538 (0.957, 2.635)	1.558 (0.988, 2.628)	1.497 (0.920, 2.642)	0.767

Abbreviations: Cl-PFESA, chlorinated polyfluorinated ether sulfonic acids; PFOS, perfluorooctane sulfonate; PFOA, perfluorooctanoic acid.
[a] Values are mean ± SD; difference tested using Student's *t*-test.
[b] Values are n (%); difference tested using Chi-square test.
[d] Gestational age < 37 weeks at delivery.
[c] Birth weight < 2500 g.
[e] Values are median (interquartile range), difference tested using Wilcoxon rank-sum test.

Table 2
Adjusted regression coefficients (95% confidence intervals) for associations of birth weight (g) and gestational age (weeks) with natural log transformed maternal serum PFAS concentrations (ln ng/mL), by infant sex.

PFAS (ln ng/mL)	Total (n = 372) β (95% CI)	Male (n = 186) β (95% CI)	Female (n = 186) β (95% CI)	$P_{interaction}$ [c]
Birth weight (g)[a]				
6:2 Cl-PFESA	−54.44 (−95.66, −13.22)	−23.96 (−84.89, 36.98)	−67.69 (−123.77, −11.61)	0.106
8:2 Cl-PFESA	−21.15(−41.44, −0.86)	−24.67 (−52.69, 3.36)	−16.36 (−45.22, 12.50)	0.684
PFOS	−83.28 (−133.20, −33.36)	−71.52 (−142.44, −0.61)	−71.91 (−143.86, 0.05)	0.678
PFOA	−73.64 (−126.39, −20.88)	−71.80 (−148.61, 5.00)	−56.04 (−129.32, 17.24)	0.958
Gestational age (weeks)[b]				
6:2 Cl-PFESA	−0.39 (−0.56, −0.22)	−0.25 (−0.51, 0.01)	−0.51 (−0.73, −0.28)	0.096
8:2 Cl-PFESA	−0.06 (−0.15, 0.03)	−0.04 (−0.16, 0.08)	−0.08 (−0.21, 0.04)	0.687
PFOS	−0.32 (−0.53, −0.11)	0.004 (−0.31, 0.32)	−0.61 (−0.90, −0.32)	0.003
PFOA	−0.21 (−0.44, 0.02)	0.17 (−0.16, 0.51)	−0.53 (−0.83, −0.23)	0.002

[a] Adjusted for gestational age, maternal age, maternal occupation, maternal education, family income, parity, and infant sex (except stratified models).
[b] Adjusted for maternal age, maternal occupation, maternal education, family income, parity, and infant sex (except stratified models).
[c] *P* for cross-product term between PFAS × infant sex entered into adjusted regression model.

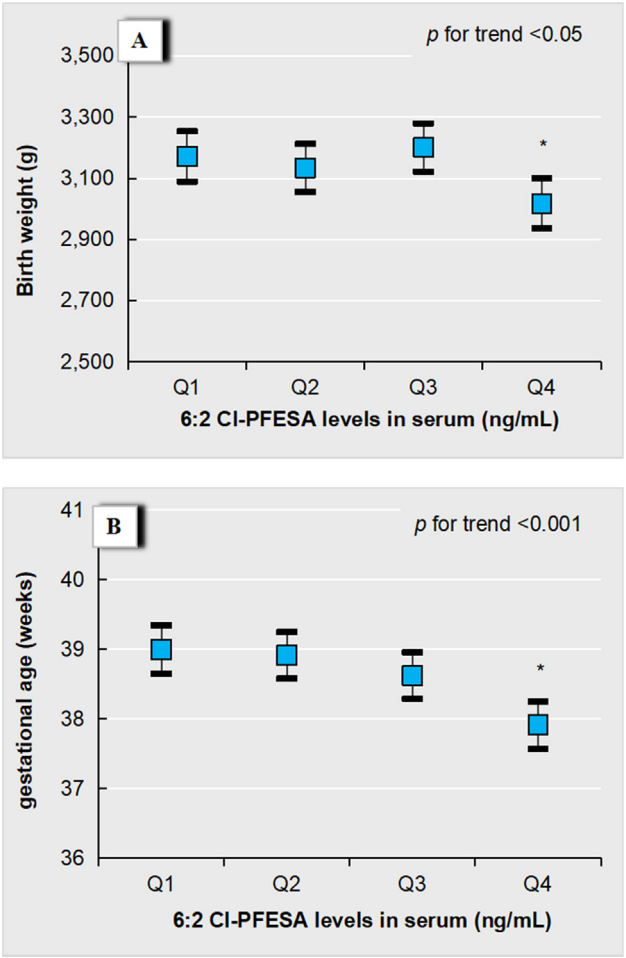

Fig. 1. Dose–response relationship between quartiles (Q) of maternal 6:2 Cl-PFESA exposure and birth weight (A) and gestational age (B) of infants (n = 93 for each quartile). The data are expressed as estimated means and the error bars depict 95% confidence intervals. Models are adjusted for infant sex, maternal age, maternal occupation, maternal education, family income, parity and gestational age (for birth weight model). *P < 0.05 compared with Q1.

6:2 Cl-PFESA and PFOS, and the associations between maternal PFAS and birth weight were similar when stratified by infant sex and without significant interactions (Table 2). However, when stratified by infant sex, the associations between maternal serum PFOS ($P_{interaction}$ = 0.003) and PFOA ($P_{interaction}$ = 0.002) with gestational age at delivery were stronger in females (β = -0.61, 95% CI:-0.90, −0.32 and β = -0.53, 95% CI:-0.83, −0.23, respectively) than in males (β = 0.004, 95% CI:-0.31, 0.32 and β = 0.17, 95% CI:-0.16, 0.51, respectively).

Table S6 lists crude regression coefficients for the associations of birth weight and gestational age with maternal PFAS. The results were generally consistent with the main analysis, although less precise, when excluding participants with GDM, gestational hypertension, and pregnancy anemia (Table S7), and also when excluding participants with GDM only (n = 27).

Table 3 describes confounder-adjusted associations of LBW with continuous and categorical maternal PFAS concentrations. We detected positive linear trends for associations of LBW with 6:2 Cl-PFESA (P = 0.047), PFOS (P < 0.001), and PFOA (P = 0.007), and with a significant positive association for continuous PFOS (OR = 2.43, 95% CI: 1.08, 5.47), although not for individual exposure quartiles.

Table 3 also describes confounder-adjusted associations of preterm birth with continuous and categorical maternal PFAS concentrations. We detected 2.67-fold (95% CI: 1.73, 4.15) greater odds of preterm birth per ln-ng/mL maternal serum 6:2 Cl-PFESA concentration, and a 2.03-fold (95% CI: 1.24, 3.32) greater odds for preterm birth per ln-ng/mL maternal serum PFOS concentration. Linear trends for preterm birth were likewise statistically significant, in which greater categorical maternal 6:2 Cl-PFESA (P < 0.001) and PFOS (P = 0.003) were associated with preterm birth. The ORs for preterm birth in association with the highest versus lowest quartiles of exposure were also elevated for 6:2 Cl-PFESA (OR = 5.42, 95% CI: 1.70, 17.29) and PFOS (OR = 4.99, 95% CI: 1.34, 18.56).

Table S8 shows adjusted associations of maternal serum PFAS with preterm birth classified as moderate preterm birth (32–33 weeks gestation) and late preterm birth (34–36 weeks gestation) (Shapiro-Mendoza and Lackritz, 2012). The pattern of associations was similar to those for overall preterm birth. Due to the small number of moderate preterm births, the associations were imprecise and may be overestimated.

4. Discussion

In this prospective birth cohort, we detected associations between maternal serum Cl-PFESAs concentrations and birth outcomes, suggesting a higher risk for adverse birth outcomes with greater maternal Cl-PFESAs exposure. We also found a possible threshold effect in which the risk for preterm birth was greater only for the highest quartile of 6:2 Cl-PFESA exposure. To the best of our knowledge, this study is the first to investigate associations between maternal Cl-PFESAs exposure and fetal development in a human population.

We detected 6:2 Cl-PFESA in 100% of women with late third

Table 3
Adjusted odds ratios (OR) and 95% confidence intervals for associations of low birth weight (< 2500 g) and preterm birth (< 37 weeks) with natural log transformed maternal serum PFAS concentrations.

PFAS	Low birth weight Adjusted OR (95%CI) [a]	Preterm birth Adjusted OR (95%CI)[b]
6:2 Cl-PFESA		
Per in ln ng/mL greater	1.54 (0.82, 2.89)	2.67 (1.73, 4.15)
Quartile (ng/mL)		
≤1.22	1.00 (reference)	1.00 (reference)
> 1.22 to 2.41	1.25 (0.21, 7.35)	0.57 (0.12, 2.70)
> 2.41 to 4.69	0.35 (0.05, 2.44)	2.19 (0.64, 7.53)
> 4.69	3.11 (0.65, 14.90)	5.42 (1.70, 17.29)
P for trend[c]	0.047	< 0.001
8:2 Cl-PFESA		
Per in ln ng/mL greater	1.12 (0.86, 1.46)	1.07 (0.90, 1.27)
Quartile (ng/mL)		
≤LOD	1.00 (reference)	1.00 (reference)
> LOD to 0.039	0.64 (0.22, 1.87)	1.02 (0.51, 2.04)
> 0.039	1.56 (0.53, 4.55)	0.99 (0.49, 1.98)
P for trend[c]	0.076	0.721
PFOS		
Per in ln ng/mL greater	2.43 (1.08, 5.47)	2.03 (1.24, 3.32)
Quartile (ng/mL)		
≤4.36	1.00 (reference)	1.00 (reference)
> 4.36 to 7.15	0.83 (0.11, 6.47)	2.22 (0.55, 9.05)
> 7.15 to 11.93	1.41 (0.23, 8.82)	4.52 (1.21, 16.88)
> 11.93	3.70 (0.61, 22.58)	4.99 (1.34, 18.56)
P for trend[c]	< 0.001	0.003
PFOA		
Per in ln ng/mL greater	1.16 (0.52, 2.58)	1.49 (0.94, 2.36)
Quartile (ng/mL)		
≤0.96	1.00 (reference)	1.00 (reference)
> 0.96 to 1.54	0.61 (0.14, 2.69)	0.71 (0.23, 2.14)
> 1.54 to 2.63	0.27 (0.05, 1.42)	1.60 (0.60, 4.23)
> 2.63	1.00 (0.23, 4.35)	1.84 (0.72, 4.71)
P for trend[c]	0.007	0.273

[a] Adjusted for gestational age, infant sex, maternal age, maternal occupation, maternal education, family income and parity.
[b] Adjusted for infant sex, maternal age, maternal occupation, maternal education, family income and parity.
[c] Tested using the median value for each category.

trimester pregnancies. We found 6:2 Cl-PFESA concentrations comparable to two previous cohorts from Wuhan, China, including 32 pregnant women in 2015–2016 with a median 1.54 ng/mL (Chen et al., 2017) and 100 pregnant women in 2014 with a median 1.90 ng/mL (Pan et al., 2017). In contrast, we detected fewer women with 8:2 Cl-PFESA in our study than from the prior Wuhan studies, which reported 84.4% (Chen et al., 2017) and 100% (Pan et al., 2017) detected, and the detection limits were 10-fold and 50-fold higher than our own. The inconsistency in 8:2 Cl-PFESA exposure might be due in part to differences in regional industries and exposure patterns, but additional investigation is necessary for a clearer understanding.

The bioaccumulation potential and toxicity of 6:2 Cl-PFESA and 8:2 Cl-PFESA were similar to or greater than PFOS in animal studies (Shi et al., 2016, Cui et al., 2018b, Zhang et al., 2018). Observational human research suggests that 6:2 Cl-PFESA is more bio-persistent than PFOS, with median total elimination half-lives of 15.3 and 6.7 years, respectively (Shi et al., 2016). There also appears to be greater placental transfer efficiency for 8:2 Cl-PFESA compared with PFOS, for which cord serum to maternal serum concentration ratios of 0.557 and 0.399 were reported, respectively (Chen et al., 2017). A more comprehensive future investigation of exposure sources will be necessary to more clearly characterize the toxicokinetics of Cl-PFESAs during pregnancy.

To date, there are no human data available to assess the reproductive toxicity of Cl-PFESAs. However, the results of several animal studies suggest a potential health risk for offspring. More than half (58.4%) of 6:2 Cl-PFESA accumulated in the ovary of the black spotted frog (Cui et al., 2018b). Zebrafish embryos incubated with various 6:2 Cl-PFESA concentrations showed delayed hatching, malformations, and reduced survival indicative of developmental toxicity (Shi et al., 2017). Mature zebrafish chronically exposed to 6:2 Cl-PFESA had offspring with poorer survival, more structural malformation, inhibited growth, decreased gonadosomatic development, greater serum testosterone levels, and thyroid hormone disruption compared to unexposed controls (Shi et al., 2018, Shi et al., 2019). However, the serum reproductive hormone levels and testicular mRNA of adult male BALB/c mice were unaffected by 56 days of 6:2 Cl-PFESA exposure (Zhou et al., 2018). Furthermore, chicken embryo survival and hatchling body mass were not affected by Cl-PFESAs injected into ova before incubation (Briels et al., 2018).

In this study, we found statistically significant associations between maternal serum concentrations of 6:2 Cl-PFESA, 8:2 Cl-PFESA, PFOS, and PFOA with birth outcomes. Ours appears to be the first study to report on birth outcomes in associations with Cl-PFESAs, but many studies have reported on associations of PFOS and PFOA with birth outcomes. Our PFOS and PFOA findings are in line with the results of several recent systematic reviews and meta-analyses, lending credibility to our Cl-PFESA results. A recent meta-analysis (Negri et al., 2017) reported pooled linear regression coefficients of −46.1 g (95% CI: −80.3, −11.9) and −27.1 g (95% CI: −50.6, −3.6) for birth weight, per ln-ng/mL greater prenatal PFOS (eight studies) and PFOA (nine studies), respectively, which were more modest than but consistent with our results. Also consistent with our results, greater PFOS concentration measured in 1645 early U.S. gravidas, recruited 1999–2002, was associated with higher odds of preterm birth ($OR_{Q1\ vs.\ Q4}$ = 2.4, 95% CI: 1.3, 4.4) (Sagiv et al., 2018). However, the relation between human PFAS exposure and birth outcomes remains controversial, given concerns about effective dose and reverse causality on the part of some investigators (Olsen et al., 2009, Verner et al., 2015). Furthermore, the results may differ across studies due to differences in timing sample collections, different modeling approaches, and adjustment for different confounding factors (Steenland et al., 2018). We found that investigators adjusted for different confounding factors in a review of 14 previous epidemiologic studies of PFOS exposure and birth outcomes (Table S9). For example, a Spanish birth cohort study reported no association between maternal PFOS and birth weight in 1202 newborns using the same statistical method that we used, but without adjustment for socioeconomic status (Manzano-Salgado et al., 2017).

Though the mechanisms by which Cl-PFESAs might affect fetal growth are unclear, several biologic effects were reported in the literature that may contribute to adverse outcome pathways. In an *in vitro* investigation, 6:2 Cl-PFESA was cytotoxic to human liver cells and bound human liver fatty acid binding protein (hL-FABP), which affects lipid metabolism and fatty acid transportation (Sheng et al., 2018). Studies *in vitro* and *in vivo* indicated that Cl-PFESAs activated peroxisome proliferator-activated receptors (PPARs) to affect lipid metabolism, with 8:2 Cl-PFESA having greater PPAR signaling pathway agonistic activity than PFOS (Li et al., 2018, Shi et al., 2019). Similar to the reports for PFOS (Ballesteros et al., 2017, Coperchini et al., 2017, Zeng et al., 2019), Cl-PFESAs also behave as endocrine disruptors, as thyroid receptor agonistic activity led to thyroid hormone disorders in a study of zebrafish larvae (Deng et al., 2018). Thyroid hormones play an important role in fetal growth and development (Forhead and Fowden, 2014).

We also found stronger associations between PFAS and gestational age among female infants than among males in this study. The reason for a sex-difference remains unknown but may involve interactions between PFAS and sex-steroid hormone receptors. *In vitro* studies suggest that several PFAS activate estrogen receptors and antagonize androgen receptor activity (Benninghoff et al., 2011, Kjeldsen and Bonefeld-Jorgensen, 2013). Alternately, the sex-interaction may be a chance finding. Additional research with a larger sample size is needed to clarify the influence of sex on the associations between PFAS exposure and fetal growth.

There are several strengths to this study. Firstly, we prospectively collected biomarkers of exposure during gestation, ensuring temporality of the exposure-outcome association and precluding introduction of exposure recall errors. Given the extensive half-lives of Cl-PFESAs, PFOS, and PFOA, which are measured in years, serum concentrations are likely to be reasonably representative of exposure across gestation. Secondly, we obtained birth outcomes from medical records, which also precluded recall biases and minimized outcome misclassification. Thirdly, we collected and controlled for a comprehensive panel of potential confounding variables, including sociodemographic and clinical factors. Finally, our study is the first, to our knowledge, to explore the associations of Cl-PFESAs with fetal growth and to report associations between greater gestational Cl-PFESAs exposure and a higher risk for adverse birth outcomes.

However, there are several limitations to this study. Firstly, our study population comprised only 372 pregnancies, so we may have been unable to detect modest associations and some effect estimates were imprecise. Secondly, though our analyses included key confounding variables, we did not adjust for glomerular filtration rate (GFR), which might introduce exposure misclassification due to pregnancy-associated plasma volume expansion and changes in renal clearance (Ouzounian and Elkayam, 2012). Higher GFR may lead to lower PFAS transfer efficiency (Pan et al., 2017), and GFR may itself influence birth weight (Verner et al., 2015). Thus, changes in GFR may contribute in part to associations between PFAS body burdens and fetal growth (Verner et al., 2015). However, there is inconsistent and limited information available about the influence of maternal GFR on this association (Johnson et al., 2014; Manzano-Salgado et al., 2017). Thirdly, we did not consider various other pollutants that may affect birth outcomes, such as phthalates (Bloom et al., 2019), trace elements (Freire et al., 2019; Bloom et al., 2015), and polychlorinated biphenyls (PCBs) (Lenters et al., 2019), which might have impacted PFAS associations in a synergistic or antagonistic manner (Braun et al., 2016). Likewise, given strong intercorrelations among the measured PFAS, we evaluated each in isolation and were unable to evaluate their interactions. Still, the associations for Cl-PFESAs with gestational age remained similar after further adjustment for PFOS and PFOA, although birth weight associations were attenuated. Thus, we cannot rule out the possibility for confounding by PFOA, PFOS, or other correlated PFAS, and so a larger future study that employs a formal analysis of PFAS mixtures will be necessary for more definitive results. Fourthly, we captured serum PFAS concentrations at a single time point during the study pregnancy, which may have misclassified exposure for some women, in particular given uncertainties about causal windows and changes in plasma volume and serum binding proteins throughout gestation that might alter circulating concentrations of persistent organic pollutants like PFAS (Bloom et al., 2007). Yet, given their persistent nature, with median elimination half-lives estimated as 15.3 years for 6:2 Cl-PFESA and 6.7 years for PFOS (Shi et al., 2016), the impact is difficult to predict. Fifthly, we imputed values below detection limits using a commonly employed, yet somewhat controversial approach (i.e., LOD/$\sqrt{2}$) (Richardson and Ciampi, 2003, Schisterman et al., 2006, Huynh et al., 2014). This approach may have biased associations between 8:2 Cl-PFESA, for which relatively few values were measured above the LOD, and birth outcomes. However, our results were similar, although modestly stronger for gestational age, when we repeated the analysis using machine-read values without imputation (Table S10). Finally, we conducted multiple statistical tests, which may have led to false positive results secondary to type-1 error inflation (Goldberg and Silbergeld, 2011). As an exploratory investigation, our aim was to maximize sensitivity for detecting plausible hypotheses for confirmation in a larger future investigation.

5. Conclusion

We found that Cl-PFESAs exposure in utero were associated with adverse birth outcomes, and more specifically that maternal 6:2 Cl-PFESA was positively associated with preterm birth. Yet, our study was based at a single hospital that treated gravidas from the local and surrounding areas and included only live born singletons. Thus, our results may not be generalizable to other source populations. Additional, larger investigations in multiple regions will be required for more definitive results in the future. The safety of Cl-PFESAs should be questioned, and Cl-PFESAs exposure must be merits attention from academic scientists and policy-makers.

CRediT authorship contribution statement

Chu Chu: Data curation, Formal analysis, Writing - original draft. **Yang Zhou:** Methodology, Investigation, Writing - original draft. **Qing-Qing Li:** Methodology, Formal analysis, Investigation. **Michael S. Bloom:** Methodology, Resources, Writing - review & editing. **Shao Lin:** Resources, Validation. **Yun-Jiang Yu:** Validation, Data curation. **Da Chen:** Visualization. **Hong-Yao Yu:** Investigation. **Li-Wen Hu:** Formal analysis, Funding acquisition. **Bo-Yi Yang:** Formal analysis, Funding acquisition. **Xiao-Wen Zeng:** Methodology, Visualization. **Guang-Hui Dong:** Conceptualization, Supervision, Project administration, Funding acquisition.

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Declaration of Competing Interest

All authors declare they have no actual or potential relationships that could be construed as a conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.105365.

References

U.S. Environmental Protection Agency, 2006. Letter Inviting Participation in the PFOA Stewardship Program. From https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/letter-inviting-participation-pfoa-stewardship-program.

Aylward, Glen P., 2014. Neurodevelopmental outcomes of infants born prematurely. J. Dev. Behav. Pediatr. 35 (6), 394–407.

Bach, C.C., Bech, B.H., Brix, N., Nohr, E.A., Bonde, J.P., Henriksen, T.B., 2015. Perfluoroalkyl and polyfluoroalkyl substances and human fetal growth: a systematic review. Crit. Rev. Toxicol. 45 (1), 53–67.

Ballesteros, V., Costa, O., Iniguez, C., Fletcher, T., Ballester, F., Lopez-Espinosa, M.J., 2017. Exposure to perfluoroalkyl substances and thyroid function in pregnant women and children: a systematic review of epidemiologic studies. Environ. Int. 99, 15–28.

Benninghoff, A.D., Bisson, W.H., Koch, D.C., Ehresman, D.J., Kolluri, S.K., Williams, D.E., 2011. Estrogen-like activity of perfluoroalkyl acids in vivo and interaction with human and rainbow trout estrogen receptors in vitro. Toxicol. Sci. 120 (1), 42–58.

Benskin, J.P., Ikonomou, M.G., Woudneh, M.B., Cosgrove, J.R., 2012. Rapid characterization of perfluoralkyl carboxylate, sulfonate, and sulfonamide isomers by high-performance liquid chromatography-tandem mass spectrometry. J. Chromatogr. A 1247, 165–170.

Blencowe, H., Cousens, S., Oestergaard, M.Z., Chou, D., Moller, A.-B., Narwal, R., Adler, A., Vera Garcia, C., Rohde, S., Say, L., Lawn, J.E., 2012. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. The Lancet 379 (9832), 2162–2172.

Bloom, M.S., Wenzel, A.G., Brock, J.W., Kucklick, J.R., Wineland, R.J., Cruze, L., Unal, E.R., Yucel, R.M., Jiyessova, A., Newman, R.B., 2019. Racial disparity in maternal

phthalates exposure; Association with racial disparity in fetal growth and birth outcomes. Environ. Int. 127, 473–486.
Bloom, M.S., Buck Louis, G.M., Schisterman, E.F., Liu, A., Kostyniak, P.J., 2007. Maternal serum polychlorinated biphenyl concentrations across critical windows of human development. Environ. Health Perspect. 115 (9), 1320–1324.
Bloom, M.S., Buck Louis, G.M., Sundaram, R., Maisog, J.M., Steuerwald, A.J., Parsons, P.J., 2015. Birth outcomes and background exposures to select elements, the Longitudinal Investigation of Fertility and the Environment (LIFE). Environ. Res. 138, 118–129.
Braun, J.M., Gennings, C., Hauser, R., Webster, T.F., 2016. What can epidemiological studies tell us about the impact of chemical mixtures on human health? Environ. Health Perspect. 124 (1), A6–A9.
Briels, N., Ciesielski, T.M., Herzke, D., Jaspers, V.L.B., 2018. Developmental toxicity of perfluorooctanesulfonate (PFOS) and its chlorinated polyfluoroalkyl ether sulfonate alternative F-53B in the domestic chicken. Environ. Sci. Technol. 52 (21), 12859–12867.
Chen, F., Yin, S., Kelly, B.C., Liu, W., 2017. Chlorinated polyfluoroalkyl ether sulfonic acids in matched maternal, cord, and placenta samples: a study of transplacental transfer. Environ. Sci. Technol. 51 (11), 6387–6394.
Coperchini, F., Awwad, O., Rotondi, M., Santini, F., Imbriani, M., Chiovato, L., 2017. Thyroid disruption by perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA). J. Endocrinol. Invest. 40 (2), 105–121.
Crump, C.S.K., Sundquist, J., Winkleby, M.A., 2011. Gestational age at birth and mortality in young adulthood. JAMA 306 (11), 1233–1240.
Cui, Q., Pan, Y., Zhang, H., Sheng, N., Dai, J., 2018a. Elevated concentrations of perfluorohexanesulfonate and other per- and polyfluoroalkyl substances in Baiyangdian Lake (China): source characterization and exposure assessment. Environ. Pollut. 241, 684–691.
Cui, Q., Pan, Y., Zhang, H., Sheng, N., Wang, J., Guo, Y., Dai, J., 2018b. Occurrence and tissue distribution of novel perfluoroether carboxylic and sulfonic acids and legacy per/polyfluoroalkyl substances in black-spotted frog (Pelophylax nigromaculatus). Environ. Sci. Technol. 52 (3), 982–990.
Deng, M., Wu, Y., Xu, C., Jin, Y., He, X., Wan, J., Yu, X., Rao, H., Tu, W., 2018. Multiple approaches to assess the effects of F-53B, a Chinese PFOS alternative, on thyroid endocrine disruption at environmentally relevant concentrations. Sci. Total Environ. 624, 215–224.
Forhead, A.J., Fowden, A.L., 2014. Thyroid hormones in fetal growth and prepartum maturation. J. Endocrinol. 221 (3), R87–R103.
Freire, C., Amaya, E., Gil, F., Murcia, M., LLop, S., Casas, M., Vrijheid, M., Lertxundi, A., Irizar, A., Fernández-Tardón, G., Castro-Delgado, R.V., 2019. Placental metal concentrations and birth outcomes: the environment and childhood (INMA) project. Int. J. Hyg. Environ. Health 222 (3), 468–478.
Fromme, H., Tittlemier, S.A., Volkel, W., Wilhelm, M., Twardella, D., 2009. Perfluorinated compounds–exposure assessment for the general population in Western countries. Int. J. Hyg. Environ. Health 212 (3), 239–270.
Gebbink, W.A., Bossi, R., Riget, F.F., Rosing-Asvid, A., Sonne, C., Dietz, R., 2016. Observation of emerging per- and polyfluoroalkyl substances (PFASs) in Greenland marine mammals. Chemosphere 144, 2384–2391.
Goldberg, M., Silbergeld, E., 2011. On multiple comparisons and on the design and interpretation of epidemiological studies of many associations. Environ. Res. 111 (8), 1007–1009.
Greenland, S., Pearl, J., Robins, J.M., 1999. Causal diagrams for epidemiologic research. Epidemiology 10 (1), 37–48.
Hornung, R.W.R., Laurence, D., 1990. Estimation of average concentration in the presence of nondetectable values. Appl. Occup. Environ. Hyg. 5 (1), 46–51.
Huynh, T., Ramachandran, G., Banerjee, S., Monteiro, J., Stenzel, M., Sandler, D.P., Engel, L.S., Kwok, R.K., Blair, A., Stewart, P.A., 2014. Comparison of methods for analyzing left-censored occupational exposure data. Ann. Occup. Hyg. 58 (9), 1126–1142.
Johnson, P.I., Sutton, P., Atchley, D.S., Koustas, E., Lam, J., Sen, S., Robinson, K.A., Axelrad, D.A., Woodruff, T.J., 2014. The Navigation Guide - evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. Environ. Health Perspect. 122 (10), 1028–1039.
Kato, K., Kalathil, A.A., Patel, A.M., Ye, X., Calafat, A.M., 2018. Per- and polyfluoroalkyl substances and fluorinated alternatives in urine and serum by on-line solid phase extraction-liquid chromatography-tandem mass spectrometry. Chemosphere 209, 338–345.
Kjeldsen, L.S., Bonefeld-Jorgensen, E.C., 2013. Perfluorinated compounds affect the function of sex hormone receptors. Environ. Sci. Pollut. Res. Int. 20 (11), 8031–8044.
Lee, A.I., Okam, M.M., 2011. Anemia in pregnancy. Hematol. Oncol. Clin. North Am. 25 (2), 241–259.
Lenters, V., Iszatt, N., Forns, J., Cechova, E., Kocan, A., Legler, J., Leonards, P., Stigum, H., Eggesbo, M., 2019. Early-life exposure to persistent organic pollutants (OCPs, PBDEs, PCBs, PFASs) and attention-deficit/hyperactivity disorder: a multi-pollutant analysis of a Norwegian birth cohort. Environ. Int. 125, 33–42.
Li, C.H., Ren, X.M., Ruan, T., Cao, L.Y., Xin, Y., Guo, L.H., Jiang, G., 2018. Chlorinated polyfluorinated ether sulfonates exhibit higher activity toward peroxisome proliferator-activated receptors signaling pathways than perfluorooctanesulfonate. Environ. Sci. Technol. 52 (5), 3232–3239.
Li, M., Zeng, X.W., Qian, Z.M., Vaughn, M.G., Sauve, S., Paul, G., Lin, S., Lu, L., Hu, L.W., Yang, B.Y., Zhou, Y., Qin, X.D., Xu, S.L., Bao, W.W., Zhang, Y.Z., Yuan, P., Wang, J., Zhang, C., Tian, Y.P., Nian, M., Xiao, X., Fu, C., Dong, G.H., 2017. Isomers of perfluorooctanesulfonate (PFOS) in cord serum and birth outcomes in China: Guangzhou birth cohort study. Environ. Int. 102, 1–8.
Lin, Y., Liu, R., Hu, F., Liu, R., Ruan, T., Jiang, G., 2016. Simultaneous qualitative and quantitative analysis of fluoroalkyl sulfonates in riverine water by liquid chromatography coupled with Orbitrap high resolution mass spectrometry. J. Chromatogr. A 1435, 66–74.
Liu, L.Y., Ma, W.L., Jia, H.L., Zhang, Z.F., Song, W.W., Li, Y.F., 2016. Research on persistent organic pollutants in China on a national scale: 10 years after the enforcement of the Stockholm Convention. Environ. Pollut. 217, 70–81.
Maisonet, M., Terrell, M.L., McGeehin, M.A., Christensen, K.Y., Holmes, A., Calafat, A.M., Marcus, M., 2012. Maternal concentrations of polyfluoroalkyl compounds during pregnancy and fetal and postnatal growth in British girls. Environ. Health Perspect. 120 (10), 1432–1437.
Malik, R., Kumar, V., 2017. Hypertension in pregnancy. Adv. Exp. Med. Biol. 956, 375–393.
Manzano-Salgado, C.B., Casas, M., Lopez-Espinosa, M.J., Ballester, F., Iniguez, C., Martinez, D., Costa, O., Santa-Marina, L., Pereda-Pereda, E., Schettgen, T., Sunyer, J., Vrijheid, M., 2017. Prenatal exposure to perfluoroalkyl substances and birth outcomes in a Spanish birth cohort. Environ. Int. 108, 278–284.
Metzger, B.E., Gabbe, S.G., Persson, B., Buchanan, T.A., Catalano, P.A., Damm, P., Dyer, A.R., Leiva, A., Hod, M., Kitzmiler, J.L., Lowe, L.P., McIntyre, H.D., Oats, J.J., Omori, Y., Schmidt, M.I., 2010. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 33 (3), 676–682.
Mohammad, K., Kassab, M., Gamble, J., Creedy, D.K., Foster, J., 2014. Factors associated with birth weight inequalities in Jordan. Int. Nurs. Rev. 61 (3), 435–440.
Nardozza, L.M., Caetano, A.C., Zamarian, A.C., Mazzola, J.B., Silva, C.P., Marcal, V.M., Lobo, T.F., Peixoto, A.B., Araujo Junior, E., 2017. Fetal growth restriction: current knowledge. Arch. Gynecol. Obstet. 295 (5), 1061–1077.
Negri, E., Metruccio, F., Guercio, V., Tosti, L., Benfenati, E., Bonzi, R., La Vecchia, C., Moretto, A., 2017. Exposure to PFOA and PFOS and fetal growth: a critical merging of toxicological and epidemiological data. Crit. Rev. Toxicol. 47 (6), 489–515.
Olsen, G.W., Butenhoff, J.L., Zobel, L.R., 2009. Perfluoroalkyl chemicals and human fetal development: an epidemiologic review with clinical and toxicological perspectives. Reprod. Toxicol. 27 (3–4), 212–230.
Ouzounian, J.G., Elkayam, U., 2012. Physiologic changes during normal pregnancy and delivery. Cardiol. Clin. 30 (3), 317–329.
Pan, Y., Zhang, H., Cui, Q., Sheng, N., Yeung, L.W.Y., Sun, Y., Guo, Y., Dai, J., 2018. Worldwide distribution of novel perfluoroether carboxylic and sulfonic acids in surface water. Environ. Sci. Technol. 52 (14), 7621–7629.
Pan, Y., Zhu, Y., Zheng, T., Cui, Q., Buka, S.L., Zhang, B., Guo, Y., Xia, W., Yeung, L.W., Li, Y., Zhou, A., Qiu, L., Liu, H., Jiang, M., Wu, C., Xu, S., Dai, J., 2017. Novel chlorinated polyfluorinated ether sulfonates and legacy per-/polyfluoroalkyl substances: placental transfer and relationship with serum albumin and glomerular filtration rate. Environ. Sci. Technol. 51 (1), 634–644.
Pocobelli, G., Dublin, S., Enquobahrie, D.A., Mueller, B.A., 2016. Birth weight and birth weight for gestational age in relation to risk of hospitalization with primary hypertension in children and young adults. Matern. Child Health J. 20 (7), 1415–1423.
Richardson, D.B., Ciampi, A., 2003. Effects of exposure measurement error when an exposure variable is constrained by a lower limit. Am. J. Epidemiol. 157 (4), 355–363.
Ruan, T., Lin, Y., Wang, T., Liu, R., Jiang, G., 2015. Identification of novel polyfluorinated ether sulfonates as PFOS alternatives in municipal Sewage Sludge in China. Environ. Sci. Technol. 49 (11), 6519–6527.
Sagiv, S.K., Rifas-Shiman, S.L., Fleisch, A.F., Webster, T.F., Calafat, A.M., Ye, X., Gillman, M.W., Oken, E., 2018. Early-pregnancy plasma concentrations of perfluoroalkyl substances and birth outcomes in project viva: confounded by pregnancy hemodynamics? Am. J. Epidemiol. 187 (4), 793–802.
Saigal, S., Doyle, L.W., 2008. An overview of mortality and sequelae of preterm birth from infancy to adulthood. The Lancet 371 (9608), 261–269.
Savitz, D.A., 2007. Guest editorial: biomarkers of perfluorinated chemicals and birth weight. Environ. Health Perspect. 115 (11), A528–A529.
Schisterman, E.F., Vexler, A., Whitcomb, B.W., Liu, A., 2006. The limitations due to exposure detection limits for regression models. Am. J. Epidemiol. 163 (4), 374–383.
Schisterman, E.F., Cole, S.R., Platt, R.W., 2009. Overadjustment bias and unnecessary adjustment in epidemiologic studies. Epidemiology 20 (4), 488–495.
Shapiro-Mendoza, C.K., Lackritz, E.M., 2012. Epidemiology of late and moderate preterm birth. Semin Fetal Neonatal Med 17 (3), 120–125.
Sheng, N., Cui, R., Wang, J., Guo, Y., Wang, J., Dai, J., 2018. Cytotoxicity of novel fluorinated alternatives to long-chain perfluoroalkyl substances to human liver cell line and their binding capacity to human liver fatty acid binding protein. Arch. Toxicol. 92 (1), 359–369.
Shi, G., Cui, Q., Pan, Y., Sheng, N., Sun, S., Guo, Y., Dai, J., 2017. 6:2 Chlorinated polyfluorinated ether sulfonate, a PFOS alternative, induces embryotoxicity and disrupts cardiac development in zebrafish embryos. Aquat. Toxicol. 185, 67–75.
Shi, G., Cui, Q., Wang, J., Guo, H., Pan, Y., Sheng, N., Guo, Y., Dai, J., 2019. Chronic exposure to 6:2 chlorinated polyfluorinated ether sulfonate acid (F-53B) induced hepatotoxic effects in adult zebrafish and disrupted the PPAR signaling pathway in their offspring. Environ. Pollut. 249, 550–559.
Shi, G., Guo, H., Sheng, N., Cui, Q., Pan, Y., Wang, J., Guo, Y., Dai, J., 2018. Two-generational reproductive toxicity assessment of 6:2 chlorinated polyfluorinated ether sulfonate (F-53B, a novel alternative to perfluorooctane sulfonate) in zebrafish. Environ. Pollut. 243 (Pt B), 1517–1527.
Shi, Y., Vestergren, R., Xu, L., Zhou, Z., Li, C., Liang, Y., Cai, Y., 2016. Human exposure and elimination kinetics of chlorinated polyfluoroalkyl ether sulfonic acids (Cl-PFESAs). Environ. Sci. Technol. 50 (5), 2396–2404.
Steenland, K., Barry, V., Savitz, D., 2018. Serum perfluorooctanoic acid and birthweight: an updated meta-analysis with bias analysis. Epidemiology 29 (6), 765–776.
Sunderland, E.M., Hu, X.C., Dassuncao, C., Tokranov, A.K., Wagner, C.C., Allen, J.G., 2019. A review of the pathways of human exposure to poly- and perfluoroalkyl substances (PFASs) and present understanding of health effects. J Expo Sci Environ Epidemiol 29 (2), 131–147.

Tian, Y., Zhou, Y., Miao, M., Wang, Z., Yuan, W., Liu, X., Wang, X., Wang, Z., Wen, S., Liang, H., 2018. Determinants of plasma concentrations of perfluoroalkyl and polyfluoroalkyl substances in pregnant women from a birth cohort in Shanghai, China. Environ. Int. 119, 165–173.

Verner, M.A., Loccisano, A.E., Morken, N.H., Yoon, M., Wu, H., McDougall, R., Maisonet, M., Marcus, M., Kishi, R., Miyashita, C., Chen, M.H., Hsieh, W.S., Andersen, M.E., Clewell 3rd, H.J., Longnecker, M.P., 2015. Associations of perfluoroalkyl substances (PFAS) with lower birth weight: an evaluation of potential confounding by glomerular filtration rate using a physiologically based pharmacokinetic model (PBPK). Environ. Health Perspect. 123 (12), 1317–1324.

Wang, S., Huang, J., Yang, Y., Hui, Y., Ge, Y., Larssen, T., Yu, G., Deng, S., Wang, B., Harman, C., 2013. First report of a Chinese PFOS alternative overlooked for 30 years: its toxicity, persistence, and presence in the environment. Environ. Sci. Technol. 47 (18), 10163–10170.

Wang, T., Vestergren, R., Herzke, D., Yu, J., Cousins, I.T., 2016. Levels, isomer profiles, and estimated riverine mass discharges of perfluoroalkyl acids and fluorinated alternatives at the mouths of chinese rivers. Environ. Sci. Technol. 50 (21), 11584–11592.

Wang, Y., Chang, W., Wang, L., Zhang, Y., Zhang, Y., Wang, M., Wang, Y., Li, P., 2019. A review of sources, multimedia distribution and health risks of novel fluorinated alternatives. Ecotoxicol. Environ. Saf. 182, 109402.

Wang, Z., Cousins, I.T., Scheringer, M., Buck, R.C., Hungerbuhler, K., 2014. Global emission inventories for C4–C14 perfluoroalkyl carboxylic acid (PFCA) homologues from 1951 to 2030, Part I: production and emissions from quantifiable sources. Environ. Int. 70, 62–75.

WHO, 1977. WHO recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Acta Obstet. Gynecol. Scand. 56, 247–253.

Wilcox, A.J., Weinberg, C.R., Basso, O., 2011. On the pitfalls of adjusting for gestational age at birth. Am. J. Epidemiol. 174 (9), 1062–1068.

Zeng, Z., Song, B., Xiao, R., Zeng, G., Gong, J., Chen, M., Xu, P., Zhang, P., Shen, M., Yi, H., 2019. Assessing the human health risks of perfluorooctane sulfonate by in vivo and in vitro studies. Environ. Int. 126, 598–610.

Zhang, H., Zhou, X., Sheng, N., Cui, R., Cui, Q., Guo, H., Guo, Y., Sun, Y., Dai, J., 2018. Subchronic hepatotoxicity effects of 6:2 chlorinated polyfluorinated ether sulfonate (6:2 Cl-PFESA), a novel perfluorooctane sulfonate (PFOS) alternative, on adult male mice. Environ. Sci. Technol. 52 (21), 12809–12818.

Zhou, X., Wang, J., Sheng, N., Cui, R., Deng, Y., Dai, J., 2018. Subchronic reproductive effects of 6:2 chlorinated polyfluorinated ether sulfonate (6:2 Cl-PFAES), an alternative to PFOS, on adult male mice. J. Hazard. Mater. 358, 256–264.