Perfluoroalkyl Substances Exposure in Early Pregnancy and Preterm Birth in Singleton Pregnancies: A Prospective Cohort Study

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Abstract
Background: Preterm birth (PTB, < 37 completed weeks’ gestation) is one of the global public health concerns. Epidemiologic evidence on the potential impact of perfluoroalkyl substances (PFAS) on PTB is still limited and inconsistent. We aimed to investigate the associations between prenatal PFAS exposure and PTB among singleton live births.

Methods: We studied 2849 mother-infant pairs in the Shanghai Birth Cohort (SBC) from 2013 to 2016. Ten PFAS in maternal plasma in early pregnancy were measured. Primary outcomes were duration of gestation, PTB, spontaneous PTB and clinically indicated PTB. A linear regression model was used to assess the associations between ln-transformed PFAS and duration of gestation (weeks). A logistic regression model was applied to estimate the risks of these outcomes within a ln-transformed continuous PFAS concentrations and across non-transformed quartiles of PFAS concentrations. A Cox proportional hazards model was also used to examine the associations by treating PFAS as continuous ln-transformed variables.

Results: The incidence of overall PTB was 4.8% (95% confidence limit: 4.0% - 5.6%) in this study population. In the linear logistic regression analyses, PFAS were not associated with duration of gestation after controlling for potential confounders. In the multiple logistic model and Cox model analyses, no significant associations were observed between PFAS and overall PTB, spontaneous PTB or indicated PTB.

Conclusion: Our prospective cohort study shows that maternal plasma PFAS concentrations in early pregnancy was not associated with gestational length, overall PTB, spontaneous PTB or indicated PTB.

Background
Preterm birth (PTB), defined as a birth < 37 completed weeks’ gestation, is one of the global public health problems with an average rate of 10.6% around the world [1, 2]. PTB is the leading cause of neonate mortality and under-5 mortality worldwide in 2016[1]. Children with PTB are at increased risks of long-term consequences such as impaired neurodevelopmental functioning, respiratory complications and gastrointestinal diseases[3]. Despite great efforts to reduce PTB[4, 5] in many countries, the incidence has not yet been significantly reduced. PTB is a particular concern in China as
China has a minimum of 1 - 1.5 million preterm births each year and the incidence has been increasing in the past 2 - 3 decades [1, 5–7].

Environmental pollution, endocrine disrupting chemicals in particular, has been suspected to be one of the culprits of PTB[8]. For example, perfluoroalkyl substances (PFAS) are a subgroup of the widespread synthetic chemicals and environmentally persistent[9]. PFAS have excellent oil-repellent, water-repellent and dirt resistance characteristics[10]. They have been extensively used in household products (e.g., non-stick cookware, shampoo and carpets) since the 1950s[11]. Humans are exposed through oral intake, skin contact and inhalation[12].

Previous studies demonstrated that PFAS can change lipid metabolism[13], disrupt thyroid function[14], interfere glucose tolerance[13], and influences of estrogen homeostasis[15]. PFAS is, therefore, plausible to cause PTB. However, epidemiologic evidence linking PFAS with PTB or length of gestation is limited and inconsistent. Two studies based on birth cohorts reported that the upper quartile groups of perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS) exposure in early pregnancy versus the lowest quartile groups increased the odds of PTB by 1.7 fold or more [16, 17]. Another study also reported that a higher exposure level of PFOS but not PFOA in the cord blood was associated with the increased risk of PTB (odds ratio: 2.5, 95% CI: 1.5, 4.1)[18]. In contrast, several other studies did not observe any positive associations[19–22].

The current study aimed to examine the associations between the concentrations of ten PFAS in early pregnancy and duration of gestation, PTB in a large prospective cohort in Shanghai, China.

**Methods**

**Study population**

Study subjects in the current analysis were from the Shanghai Birth Cohort, a large prospective study in Shanghai, China, from 2013 to 2016[23]. Recruited couples were aged 20 years or older, married, seeking preconception care or in early pregnancy, spontaneous conception, at least one of them being registered residents in Shanghai with no plan to move out of Shanghai for two years after enrollment. Participants provided an informed consent before enrollment, and were interviewed by trained staffs to complete structured questionnaires on demographics, previous reproductive
characteristics, health diseases and lifestyle factors, and provided blood sample voluntarily at the recruitment visit. Clinically relevant characteristics of the current pregnancy such as pregnancy complications, chronic diseases during current pregnancy, the number of fetus, infant sex and gestational age at birth were extracted from hospital medical records. An ethical approval was obtained from the Ethical Committee of Xinhua Hospital affiliated to the Shanghai Jiao Tong University School of Medicine.

For the current analysis, a total of 3242 women who provided blood samples in early pregnancy and delivered a singleton live birth were initially included. Births with missing information on gestational age at birth, gestational age < 21 weeks or > 42 weeks were excluded (n = 289). Mothers or infants with missing information on maternal age at enrollment, pre-pregnancy body mass index (BMI), parental educational level, parity, chronic diseases during pregnancy or infant sex were excluded (n = 104). Finally, 2849 mother-infant pairs were included for analysis.

**PFAS measurement**

Blood samples were taken during early pregnancy and immediately centrifuged and frozen at −80 °C. A detailed analytical method has been described elsewhere[24]. In brief, PFAS concentrations were measured in 100 μl plasma using high-performance liquid chromatography/tandem mass spectrometry (HPLC/MS-MS; Agilent1290-6490, Agilent Technologies Inc., USA). The limit of detection (LOD) for PFOA and PFOS was 0.09 ng/mL, for PFDoA was 0.05 ng/mL, for PFHpA was 0.03 ng/mL, for PFDA, PFNA, PFUA and PFHxS was 0.02 ng/mL and for PFOSA was 0.12 ng/mL.

**Outcome**

PTB was defined as birth between 21 and 36 completed weeks’ gestation. Spontaneous PTB referred to spontaneous onset labor and preterm premature rupture of the membranes (PPROM) irrespective of mode of delivery (vaginal or cesarean section), while clinically indicated PTB was defined as PTB for preeclampsia, fetal stress, placenta previa and other maternal, fetal or placenta indications[3].

**Covariates**

Demographic characteristics included maternal age (< 30, 30 - 34, ≥ 35 years old), parental education levels (≤ 12, > 12 years), smoking status during the first pregnancy (no, yes, unknown), gestational age (the number of weeks between the last menstrual period and blood drawn) at blood
collection. Obstetric and medical variables included pre-pregnancy BMI (< 18.5, 18.5 - 24.9, ≥ 25 kg/m²), parity (0, ≥ 1), pregnancy complicated with chronic diseases (no, yes), infant sex (female, male). Chronic diseases included heart disease, kidney or liver disease, diabetes mellitus, chronic hypertension disorders, epilepsy, malnutrition and anemia.

Analysis

Distributions of demographic and pregnancy related characteristics were showed as numbers and percentages. PFAS with concentrations below the LOD were assigned LOD/√2. The distribution of PFAS in early pregnancy was presented as medians and interquartile ranges (IQRs).

Multivariable restricted cubic spline model was used to examine the potential non-linear relationships between PFAS and gestational age (weeks) at birth, according to the ln-transformed PFAS at three knots of 10th, 50th, 90th percentile. Univariable and multivariable linear regression analyses were used to evaluate the associations of ln-transformed PFAS with gestational age (weeks) at birth. Simple and multiple logistic regression analyses were applied to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of the overall PTB, spontaneous PTB and clinically indicated PTB. In the logistic regression models, PFAS were entered as continuous variables (ln-transformed) and in quartiles (untransformed). The lowest quartile served as the reference group. Cox proportional hazards regression models using gestational age at birth (weeks) as the time scale and censored at 37 weeks were employed to assess the risk of PTB for each ln-transformed continues PFAS exposure. Crude and adjusted hazard ratios (HRs) with 95% CIs were calculated. Based on the directed acyclic graphs and existing literatures, covariates were included in all adjusted models, including maternal age (years), pre-pregnancy BMI (kg/m²), parental education levels (≤ 12, > 12 years), parity (0, ≥ 1), chronic diseases (no, yes), infant sex (female, male) and gestational week at blood collection. Because only few mothers (n = 9, 0.3%) smoked during early pregnancy, maternal smoking status was not included in the adjusted models.

To investigate the potential modification of infant sex, we performed a stratified analysis by infant sex. To examine whether the associations differed among women who were multiparous, had preterm labor history, or complicated with chronic diseases, we carried out several subgroup analyses,
restricting to women without these diseases, respectively. All analyses were carried out using SAS version 9.4 (IBM SAS Institute Inc, Cary, NC) and R software (R version 3.6.1). Results at \( p < 0.05 \) were thought to be statistically significant.

**Results**

Of all the 2849 women included in the present study, 136 (4.8%) gave a singleton live birth before 37 weeks’ gestation, including 97 (71.3%) spontaneous PTB and 39 (28.7%) indicated PTB. More than 60% of the women aged less than 30 years and most of them were nulliparous (85.5%), nonsmokers (99.4%) and had normal weight (18.5 < BMI < 25 kg/m\(^2\)) before pregnancy (74.4%). The vast majority (95.0%) of couples had more than 12 years of education and only 197 (6.9%) women complicated with chronic diseases during pregnancy. In addition, the rate of boys and girls was 51.1% and 48.9%, respectively (Table 1).

PFOA, PFOS, PFNA, PFDA, PFUA and PFHxS were detected in all samples, whereas PFHpA, PFBS, PFDoA and PFOSA were quantified in 82.6%, 66.3%, 67.9% and 28.7%, respectively. PFBS, PFDoA and PFOSA were not included in following analyses for a low detection rate (< 70%). Median concentrations were 11.85, 9.33, 1.69, 1.69, 1.39, 0.54, and 0.06 ng/mL for PFOA, PFOS, PFNA, PFDA, PFUA, PFHxS and PFHpA, respectively (Table 2).

Non-linearity was not detected for the association between any ln-transformed PFAS and gestational age at birth (weeks) in a spline model (see Figure S1). No significant associations between ln-transformed PFAS and gestational age at birth (weeks) were observed in linear regression after adjusting for potential confounders (Table 3). In the multiple logistic regression analyses, the estimated associations between PFAS and overall PTB, spontaneous PTB, and indicated PTB were non-significant, either by treating PFAS as continuous ln-transformed variables (Table 4) or by categorizing PFAS into quartile variables (see Table S1). Moreover, the associations between PFAS and overall PTB, spontaneous PTB and indicated PTB were also not statistically significant in the multivariable Cox proportional hazards regression analyses (Table 5).

In the stratified analysis, the associations between continuous ln-transformed PFAS and overall PTB, spontaneous PTB, and indicated PTB did not differ by infant sex (see Table S2). In the subgroup
analyses, the main results remained unchanged when we restricted to women who were nulliparous or without chronic diseases (See Table S3 and S4).

Discussion
In this prospective study of 2849 mother-infant pairs, we observed no significant associations between maternal PFAS exposure in early pregnancy and the length of gestation, or the risks of overall PTB, spontaneous PTB or indicated PTB at the present exposure levels.

A previous cohort study in Denmark found that the 3 upper quartiles of PFOA and PFOS in early pregnancy relative to the first quartile were significantly associated with PTB among six PFAS (PFOA, PFOS, PFNA, PFDA, PFHxS, PFHpS) investigated [17]. However, this study was based on a combined data and samples from three sub-studies. It was, therefore, less certain whether potential biases might be introduced by the different study designs employed. Another relatively large birth cohort study (n = 1645) in Eastern Massachusetts reported that PFOS and PFNA exposures increased the risk of preterm birth[16], but the association was not significant for PFOA and PFHxS. The Taiwan Birth Panel Study included 429 mother-infant pairs to study four PFAS (PFOA, PFOS, PFNA, PFUA) and demonstrated that PFOS level was inversely associated with gestational age at birth (weeks) and associated with the increased risk of PTB[18]. However, PFAS were measured in the cord blood in that study, rendering the causality uncertain.

In contrast to the above findings, several other studies have found no evidence of associations between PFAS exposure and PTB[19–22]. A Spanish birth cohort study (n = 1202) did not observe significant associations of maternal plasma PFOA, PFOS, PFHxS and PFNA during the first trimester with PTB[19]; a cohort study conducted in Canada (n = 252) reported that maternal serum PFOA, PFOS, and PFHxS during the second trimester did not influence the risk of PTB[21]; the C8 Health Project in the United States measured the risk of PTB in a population with high PFOA exposure, still found no associations of PTB with PFOA or PFOS[22]. Our findings were consistent with these studies. It is worth noting that none of the previous studies[16–22] differentiated clinical phenotypes of PTB. Since the underlying pathophysiology of PTB differs enormously between spontaneous and indicated PTB[3], it becomes essential to distinguish between these two types of PTB. The ability to assess PFAS
exposure during early pregnancy in relation to the risk of subtypes of PTB is a notable strength of our study. Moreover, we further adopt Cox proportional hazards regression models to provide reliable estimates, while none of the previous studies[16–22] constructed time-dependent prediction models. A recurrence risk of PTB could increase by 15% to 50% among women with a previous PTB[3]. On the contrary, birth as an elimination route may lead to lower PFAS blood concentrations[25]. Similarly, PFAS concentrations tend to decrease with higher parity[25], whereas the incidence of PTB appears to increase[26]. As a consequence, potential bias may arise from previous PTB or multiparity. To address this issue, we repeated our analyses in nulliparous women. We were also able to examine the effects of PFAS in PTB by excluding women with chronic diseases. Our findings consistently suggested no association. Moreover, PFOA and PFOS are the most frequently studied compounds, whereas PFHxS, PFNA and PFUA have only been included in few studies in relation to PTB. It appeared to suggest that these PFAS were not associated with PTB, either.

Several limitations of this study are worth noting. First, our previous survey on PTB in China between 2015 and 2016 reported an incidence rate at 6.6% among live births in Shanghai[7]. The present study had a lower incidence of PTB (4.8%), which may be explained by the fact that our study did not include multiple gestation and pregnancies conceived with assisted reproductive technology, subgroups carrying a substantial risk for PTB[3, 27]. Second, we did not adjust for pregnancy hemodynamics in the analyses. Only two previous studies[16, 17] have adjusted for hemodynamic markers (plasma albumin and estimated glomerular filtration rate) in the assessment of associations between PFAS measured in early pregnancy and birth outcomes including PTB. But their results suggested that early pregnancy hemodynamics did not confound the associations. Instead, we adjusted for the gestational week at blood collection to control for the potential hemodynamic difference. The results were virtually the same. Therefore, our findings were less likely to be biased by early pregnancy hemodynamics.

Conclusions
Our study found no significant associations between maternal PFAS concentrations in early pregnancy and the length of gestation or the risk of PTB.
List Of Abbreviations
BMI, body mass index; CI, confidence interval; IQRs, interquartile ranges; LOD, limit of detection; OR, odds ratio; PTB, preterm birth; PPROM, preterm premature rupture of the membranes; PFAS, perfluoroalkyl substances; PFOA, perfluorooctane; PFOS, perfluorooctane sulfonate; PFDA, perfluorodecanoic acid; PFUA, perfluoroundecanoic acid; PFNA, perfluorononanoic acid; PFHxS, perfluorohexanesulfonate; PFHpA, perfluoroheptanoic acid; PFBS, perfluorobutane sulfonate; PFDoA, perfluorododecanoic acid; PFOSA, perfluorooctane sulfonamide.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine. All parents provided a written informed consent.

Consent for publication
Not applicable

Availability of data and materials
The dataset generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Competing interests
The authors declare that they have no competing interests.

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Authors’ contributions
JZ designed the original study. XH analyzed the data and drafted the manuscript. LZ and RH were major contributors in writing the manuscript. JZ, LF and WW substantially revised the manuscript. All authors provided critical input to the paper. All authors read and approved the final manuscript.

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Tables
Table 1. Demographic and reproductive characteristics, n = 2,849.
Table 2. The distribution of plasma concentration of PFAS (ng/mL) at the enrollment (n = 2,849).

| PFAS      | LOD     | % < LOD | 25th percentile | Median | 75th percentile |
|-----------|---------|---------|-----------------|--------|-----------------|
| PFOA      | 0.09    | 0       | 9.20            | 11.85  | 13.26           |
| PFOS      | 0.09    | 0       | 6.54            | 9.33   | 13.65           |
| PFDA      | 0.02    | 0       | 1.14            | 1.69   | 2.52            |
| PFUA      | 0.02    | 0       | 0.94            | 1.39   | 2.05            |
| PFNA      | 0.02    | 0       | 1.21            | 1.69   | 2.36            |
| PFHxS     | 0.02    | 0       | 0.42            | 0.54   | 0.69            |
| PFHpA     | 0.03    | 17.4    | 0.04            | 0.06   | 0.10            |
| PFBS      | 0.009   | 33.7    | LOD             | 0.03   | 0.05            |
| PFDoA     | 0.05    | 32.1    | LOD             | 0.13   | 0.23            |
| PFOSA     | 0.12    | 71.3    | --              | --     | --              |

Note: LOD: limit of detection; PFOA, perfluorooctanoate; PFOS, perfluorooctane sulfonate; PFDA, perfluorodecanoic acid; PFUA, perfluoroundecanoic acid; PFNA, perfluorononanoic acid; PFHxS, perfluorohexanesulfonate; PFHpA, perfluoroheptanoic acid; PFBS, perfluorobutane sulfonate; PFDoA, perfluorododecanoic acid; PFOSA, perfluoroctane sulfonamide.

Table 3. Associations between PFAS concentrations in early pregnancy and gestational age (weeks) at birth.

| PFAS (ng/ml) | β (95% CI)       | Adjusted* β (95% CI) |
|--------------|------------------|----------------------|
| PFOA         | 0.00 (-0.13, 0.14) | -0.00 (-0.14, 0.13) |
| PFNA         | 0.03 (-0.07, 0.14) | 0.03 (-0.08, 0.13) |
| PFDA         | 0.03 (-0.06, 0.12) | 0.04 (-0.05, 0.13) |
| PFUA         | 0.07 (-0.02, 0.16) | 0.06 (-0.03, 0.15) |
| PFOS         | -0.02 (-0.12, 0.08) | 0.02 (-0.08, 0.12) |
| PFHxS        | -0.02 (-0.15, 0.10) | -0.02 (-0.14, 0.11) |
| PFHpA        | 0.02 (-0.04, 0.07) | 0.02 (-0.05, 0.08) |

*BMI: body mass index; Chronic diseases including heart disease, kidney or liver disease, diabetes mellitus, chronic hypertension disorders, epilepsy, malnutrition, anemia.
Note: PFAS concentrations were measured in maternal plasma and have been ln-transformed before entering into the model.

* Adjusted for maternal age (years), pre-pregnancy BMI (kg/m²), parity (0, ≥1), parental educational levels (≤12, >12 years), pregnancy complicating with chronic diseases (no, yes), infant sex (male, female) and gestational age at blood drawn (weeks).

Table 4. Associations between PFAS concentrations in early pregnancy and preterm birth.

| PFAS (ng/ml) | Overall preterm birth | Spontaneous preterm birth | Indicated preterm birth |
|--------------|------------------------|---------------------------|-------------------------|
|              | N_preterm=136/N_term=2713 | N_preterm=97/N_term=2713 | N_preterm=39/N_term=2810 |
|              | OR (95% CI)            | aOR* (95% CI)              | OR (95% CI)              | aOR* (95% CI) |
| PFOA         | 0.93 (0.62, 1.40)      | 0.92 (0.61, 1.33)         | 0.74 (0.45, 1.20)       | 0.73 (0.45, 1.19) | 1.63 (0.78, 3.39) | 1.71 (0.80, 3.67) |
| PFNA         | 0.85 (0.61, 1.18)      | 0.86 (0.61, 1.20)         | 0.81 (0.55, 1.19)       | 0.82 (0.56, 1.22) | 0.94 (0.52, 1.71) | 0.99 (0.53, 1.86) |
| PFDA         | 0.86 (0.65, 1.14)      | 0.88 (0.66, 1.17)         | 0.79 (0.57, 1.10)       | 0.80 (0.58, 1.12) | 1.06 (0.64, 1.76) | 1.14 (0.67, 1.93) |
| PFUA         | 0.79 (0.59, 1.05)      | 0.82 (0.61, 1.10)         | 0.77 (0.55, 1.07)       | 0.78 (0.56, 1.10) | 0.83 (0.50, 1.41) | 0.93 (0.54, 1.61) |
| PFOS         | 0.88 (0.64, 1.19)      | 0.86 (0.63, 1.17)         | 0.79 (0.55, 1.14)       | 0.77 (0.53, 1.11) | 1.12 (0.65, 1.95) | 1.13 (0.64, 2.01) |
| PFHxS        | 1.16 (0.80, 1.69)      | 1.16 (0.79, 1.71)         | 1.05 (0.67, 1.65)       | 1.03 (0.65, 1.63) | 1.45 (0.76, 2.69) | 1.58 (0.82, 3.05) |
| PFHpA        | 0.96 (0.80, 1.16)      | 0.95 (0.78, 1.15)         | 0.93 (0.74, 1.16)       | 0.91 (0.72, 1.14) | 1.04 (0.74, 1.47) | 1.06 (0.74, 1.53) |

Note: PFAS concentrations were measured in maternal plasma and have been ln-transformed before entering into the model.

* Adjusted for maternal age (years), pre-pregnancy BMI (kg/m²), parity (0, ≥1), parental educational levels (≤12, >12 years), pregnancy complicating with chronic diseases (no, yes), infant sex (male, female) and gestational age at blood drawn (weeks).

Table 5. Associations between PFAS concentrations in early pregnancy and preterm birth in Cox model.
| PFAS (ng/ml) | Overall preterm birth | Spontaneous preterm | Indicated preterm birth |
|-------------|-----------------------|---------------------|------------------------|
|             | \(N^{\text{preterm}} = 136/N^{\text{term}} = 2713\) | \(N^{\text{preterm}} = 97/N^{\text{term}} = 2713\) | \(N^{\text{preterm}} = 39/N^{\text{term}} = 2713\) |
| PFOA       | HR (95% CI) aHR* (95% CI) | HR (95% CI) aHR* (95% CI) | HR (95% CI) aHR* (95% CI) |
|            | 0.92 (0.62, 1.38) 0.92 (0.61, 1.38) | 0.73 (0.45, 1.18) 0.73 (0.45, 1.17) | 1.61 (0.77, 3.36) 1.70 (0.80, 3.63) |
| PFNA       | 0.85 (0.61, 1.17) 0.86 (0.62, 1.20) | 0.81 (0.55, 1.19) 0.82 (0.56, 1.21) | 0.94 (0.51, 1.70) 0.99 (0.53, 1.86) |
| PFDA       | 0.86 (0.66, 1.13) 0.88 (0.67, 1.17) | 0.81 (0.58, 1.12) 0.81 (0.58, 1.12) | 1.05 (0.64, 1.75) 1.13 (0.67, 1.92) |
| PFUA       | 0.79 (0.60, 1.04) 0.82 (0.62, 1.10) | 0.78 (0.55, 1.07) 0.78 (0.56, 1.10) | 0.83 (0.49, 1.40) 0.92 (0.53, 1.60) |
| PFOS       | 0.87 (0.65, 1.18) 0.86 (0.63, 1.16) | 0.79 (0.55, 1.13) 0.77 (0.54, 1.11) | 1.12 (0.64, 1.94) 1.13 (0.64, 1.99) |
| PFHxS      | 1.15 (0.79, 1.66) 1.15 (0.79, 1.67) | 1.04 (0.67, 1.63) 1.02 (0.65, 1.60) | 1.44 (0.76, 2.71) 1.56 (0.82, 2.97) |
| PFHpA      | 0.96 (0.78, 1.18) 0.95 (0.76, 1.18) | 0.93 (0.72, 1.18) 0.90 (0.70, 1.17) | 1.05 (0.71, 1.55) 1.08 (0.72, 1.61) |

Note: PFAS concentrations were measured in maternal plasma and have been ln-transformed before entering into the model; Cox model: Cox proportional hazards regression model.

* Adjusted for maternal age (years), pre-pregnancy BMI (kg/m^2), parity (0, ≥1), parental educational levels (≤12, >12 years), pregnancy complicating with chronic diseases (no, yes), infant sex (male, female) and gestational age at blood drawn (weeks).

Supplemental Figure Legends

Figure S1. Associations between PFAS (ng/ml) concentrations and gestational age at birth (GA, weeks). PFAS concentrations were measured in maternal plasma in early pregnancy and have been ln-transformed before entering into the restricted cubic spline regression model. Model adjusted for maternal age, pre-pregnancy BMI, parity, parental educational levels, pregnancy complicating with chronic diseases, infant sex and gestational age at blood drawn.

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