

Levels of PFAS concentrations in the placenta and pregnancy complications

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ABSTRACT

Background: Recent research has raised concerns about the potential health effects of perfluoroalkyl and polyfluoroalkyl substances (PFAS) exposure, particularly during critical periods of development such as pregnancy. In this study, we sought to investigate the presence and potential impacts of PFAS in the placenta.

Methods: We measured 13 PFAS compounds in placental tissue samples among 50 women who gave birth at a tertiary medical center in southern Israel. The sample comprised of 10 women with pregnancy-related complications (preterm birth, preeclampsia, gestational diabetes or small-for-gestational age) and 40 women without complications individually matched to cases by age.

Results: For five (5) out of 13 PFAS compounds (Perfluorooctane Sulfonate (PFOS), perfluorooctanoic acid (PFOA), Perfluorohexanesulphonic acid (PFHxS), Perfluorononanoic acid (PFNA), Perfluorodecanoic acid (PFDA)) median concentrations were lower or comparable to placental measurements in different international populations. Geometric mean was estimated at 0.09 ng/g (90%CI:0.07;0.10) for PFOA, 0.05 ng/g for PFNA (90%CI:0.04;0.07), 0.03 ng/g for PFDA (90%CI:0.01;0.03), 0.06 ng/g for PFHxS (90%CI:0.05;0.07), 0.23 ng/g for PFOS linear measurement (90%CI:0.20;0.26) and 0.25 ng/g (90%CI:0.22;0.30) for PFOS summed concentrations that included non-linear isomers. Composite outcome of pregnancy-related complications was associated with elevated PFOA placental concentrations at an odds ratio (OR)= 1.82 (90%CI:1.06;3.13) for an increase of one quintile of PFOA value and adjusted to maternal gravidity in a conditional logistic regression.

Conclusion: This pilot study indicates a widespread exposure to multiple PFAS compounds in placental tissue of pregnant women in Israel. These findings warrant further validation through comprehensive national human biomonitoring initiatives.

1. Background

Perfluoroalkyl and polyfluoroalkyl substances (PFAS) are a large group of fluorinated substances with strong chemical and thermal stability found in the manufacturing of technical and consumer products (Buck et al., 2011). PFAS have been utilized in numerous industries in over 200 categories of application including cookware, firefighting foam and flame retardants, carpets, paints and varnishes, leather, and rubber (Glüge et al., 2020). Widespread use leads to direct and indirect exposure to these contaminating emissions in the environment, wildlife, and

humans (Buck et al., 2011).

The general public bioaccumulates PFAS by consuming PFAS-contaminated water or food, using products made with PFAS, and breathing air containing PFAS (ATSDR, 2022). PFAS can cross the placental barrier during pregnancy and transfer to the fetus (Kim et al., 2016). Breastfeeding exposes a baby to PFAS from the mother (ATSDR, 2022). The elimination of PFAS from the body is typically a gradual process, primarily occurring through excretion of urine, menstruation, blood donation, feces and the secretion of breastmilk (ATSDR, 2022). The half-lives of PFAS compounds vary significantly, and are primarily

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determined by the specific compound and chain length. These half-lives can range from 0.92 years for compounds such as Perfluorobutanoic acid (PFBA) to 5.01 years for compounds like Perfluorohexanesulphonic acid (PFHxS) (Li et al., 2022). Delivery of the placenta can lead to a decreased PFAS serum concentration as the placenta can accumulate PFAS during pregnancy (Brantsæter et al., 2013).

Several countries routinely monitor population exposure to PFAS. Since 1999, the United States examines PFAS in blood samples of a representative subsample of its population and releases its data publicly in 2-year cycles (ATSDR, 2022). In the European Union, twenty eight countries participate in the European Human Biomonitoring Initiative (HBM4EU) where 12 PFAS compounds were measured in serum samples from individuals aged 12–18 from 2014 to 2022 (HBM4EU, 2022). Through the German Environmental Survey, blood plasma levels of PFAS were traced from 2014 to 2017 and included sampling household drinking water (Duffek et al., 2020). The Canadian Health Measures Survey conducted 2-year cycles of biomonitoring from 2007 to 2017 that established PFAS baselines (Pollock et al., 2021). In Israel, a pilot study of 20 plasma samples from blood donors screened for PFAS compounds ([Exposure to PFAS per- and polyfluoroalkyl compounds Among adults in Israel, 2022](#)). An Israeli environmental survey revealed PFAS traces in groundwater and drinking water ([Survey results of the Presence of PFAS Substances in Israel Drinking Water Wells, 2022](#)).

Exposure to PFAS has been linked to cancer, immune system dysfunction, liver damage, endocrine dysfunction, reproductive harm and other adverse outcomes (ATSDR, 2018; Radke et al., 2022). Researchers investigating an association between PFAS exposure and adverse pregnancy outcomes, have been approaching an emerging consensus on hypertensive disorders, e.g., gestational hypertension and preeclampsia (Hirke et al., 2023; Preston et al., 2022; [Probable Link Evaluation of Pregnancy Induced Hypertension and Preeclampsia, 2011](#); Huang et al., 2019). A study conducted by Huang et al. determined a dose-response relationship between PFBS and pre-eclampsia (Preston et al., 2022; [Probable Link Evaluation of Pregnancy Induced Hypertension and Preeclampsia, 2011](#); Huang et al., 2019).

Furthermore, studies have consistently shown an association between PFAS and GDM, linking PFAS exposure to increased blood glucose and a higher risk of GDM in pregnant women (Wang et al., 2018; Yu et al., 2021).

The relationship between PFAS concentrations and preterm birth has been investigated in several studies. A recent review suggested a possibility of a causal association between PFAS and preterm births (Stone et al., 2021). Additionally, it has been shown that PFAS may be adversely related to birth weight (Fei et al., 2007; Hall et al., 2022), although in one study the adverse association was true only for male infants (Hall et al., 2022).

PFAS exposure is commonly evaluated through maternal blood samples. However, measuring PFAS levels in the placenta may provide a more complete and precise evaluation of the potential impacts of PFAS on fetal development. The placenta, as it is directly connected to the fetus, serves as a conduit for the transfer of PFAS across the placental barrier to the fetus.

Soroka University Medical Center (SUMC) is the only provider of tertiary services in the Southern district of Israel treating approximately 1 million residents. Nearly all hospital births in the district take place in SUMC. The obstetric population is ethnically made up of about 40 % Jewish and 60 % Bedouin-Arab. These two populations vary in their lifestyle, socioeconomic statuses, and environmental hazards that women are exposed to in their households (Karakis et al., 2015; Landau et al., 2015; Amir et al., 2018).

SUMC contains the *Negev BioBank* (NBB) (Gat, 2022), which collects, processes, and stores tissues, blood samples, and other biological specimens for patients on biobank registry. The largest collection of samples in the NBB registry are from women arriving to the obstetric emergency department at SUMC.

In this analysis, we aimed to estimate concentrations of PFAS

compounds in placenta of 50 women giving birth in SUMC and explore effects of PFAS on pregnancy complications, specifically, preterm birth, preeclampsia, gestational diabetes or small-for-gestational age.

2. Methods

2.1. Study population

We enrolled women who gave birth in SUMC during the period Dec 2018–Jun 2021 and participated in the NBB registry with collected placenta samples. To ensure maximum homogeneity of the study sample and enhance analysis efficiency, our inclusion criteria were limited to women of Jewish ethnicity.

2.2. Study design

The study was conducted in a case-control format, where the placenta samples in the study population were divided into samples from women with pregnancy and/or birth adverse outcomes and their healthy controls, matched by age at delivery. The complications were defined as a composite of gestational diabetes, and/or preeclampsia, as well as newborns born preterm and/or diagnosed with small-for-gestational age (SGA). Specifically, out of 244 women eligible for the study, we randomly chose 10 women with adverse perinatal outcomes (cases) and individually matched them to healthy subjects at a ratio of 1:4, comprising a total of 50 subjects participating in the analysis.

We used the information from the SUMC medical charts and women's records by their primary physicians to ascertain their clinical status. The electronic database at SUMC also contained comprehensive information on maternal chronic morbidities prior to delivery.

The study protocol has been approved by the local IRB committee of the Soroka University Medical Center, approval number 216–21-SOR.

2.3. Testing procedures

Post-delivery, the placenta was collected and fragmented pieces were immediately deposited into cryovials and stored in a liquid nitrogen bath for quick freezing. The placenta samples were frozen at a -19.6°C temperature upon their collection by the NBB personnel and later delivered to the Human Biomonitoring (HBM) Unit of the Israel National Public Health Laboratory, for testing. The samples were assessed for placental concentrations of 13 PFAS individual chemicals, including two of the most studied chemicals in this group, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), according to a modified procedure described by Vela-Soria et al (Vela-Soria et al., 2021). Weighted amount of placenta samples (100–500 mg) after enzymatic liquefaction were spiked with isotopically labeled PFAS analogs and extracted with hexane saturated acetonitrile in the presence of NaCl. After supernatant evaporation under Nitrogen, the residue was redissolved in 6 % sodium chloride solution and acidified with HCl (1:1) to pH2. PFAS were extracted by 2 portions of MTBE. The final extract was evaporated to dryness under Nitrogen and redissolved in 500 μL of MeOH: 2 mM ammonium acetate (1:1) and tested by LC-MS/MS.

LC-MS/MS analysis was performed using Water Xevo TQ-S Instrument (Water Corporation, Milford, MA, USA) according to procedure developed by Water Corporation (Organtini et al., 2020). PFAS quantification was done using both, water and matrix (placenta) internal standard calibration procedures (by isotope dilution technique). Matrix calibration curves were obtained from pooled homogenized placenta sample (portions of 300–350 mg spiked with all tested compounds at concentration range 0.01–2 ng/g). Due to the presence of baseline levels of PFOS, PFOA, and PFNA in pooled placenta samples, it was unfeasible to employ matrix match calibration for these compounds within the 0.01–0.5 ng/g range. To address this issue, suitable calibration curves were prepared using PFAS solutions in a water/acetonitrile mixture. Positive quality control samples (QCS) were generated by spiking real

placenta samples with the tested compounds (at a concentration of 0.5 ng/g) as well as acetonitrile PFAS solutions (ranging from 0.1 to 0.5 µg/l to simulate placenta concentrations of 0.03–0.15 ng/g). These QCS were subjected to the same testing procedure as the regular samples, including the sample preparation step. Method limits of quantification (LOQ) were established by validation procedure (from spiked placenta sample) as following: 0.067 ng/g (PFBA, PFPeA, PFHxA, PFOA, PFUnDA, PFHxS, PFHpS) and 0.03 ng/g (PFHpA, PFNA, PFDA, PFDoDA, PFBS, PFOS).

Blank samples were included to test for contamination of sample collection materials and all procedure steps.

2.4. Statistical analysis

The continuous variables were described by means±standard deviation (sd), median, minimum, and maximum and compared between the study groups using a t-test or Wilcoxon test, depending on their distribution. Categorical variables were presented by their percentage out of available cases and compared between study groups using a Chi-Square or Fisher Exact test.

The placental concentrations of PFAS chemicals were presented per sample weight in grams, calculated as the sample concentration divided by its weight. When concentrations were below the level of detection, the concentration values were imputed by the level of quantification (LOQ) relevant for each compound divided by the square root of 2. In attempt to aggregate the PFAS chemicals in one measure, we used the methodology suggested by Liu et al. (2022), resulting in a PFAS exposure burden score. 2-(N-methyl-perfluorooctane sulfonamido) acetic acid (Me-PFOSA-AcOH), was one out of the 8 chemicals comprising the score that was not measured in our analysis; and therefore, its values were set to missing in calculation of PFAS burden. The other chemicals used for the burden score calculation included: PFUA, PFDeA, PFHxS, PFNA, PFOA and two isomers of PFOS, linear and summed with non-linear isomers.

We calculated the percent of samples above the LOQ. Estimates of geometric mean, median, and maximal values were calculated for compounds with at least 10 % detection in the total study sample. We then compared the two study groups using a log t test. To account for the uncertainty in PFAS placental concentrations in samples with weight less than 300 mg, we performed the analysis separately for samples weighing less and weighing more than 300 mg. Upon obtaining similar directions for both strata, the final analysis was performed on a pooled sample, and included adjustment to indicator of a sample weight below or beyond 300 mg.

In the main analysis, we compared exposure to PFAS chemicals between the study groups, using conditional logistic regression and accounting for matched subjects as clusters. In this analysis, the PFAS concentrations were divided into quintiles. The estimates of the association between PFAS quintiles and pregnancy-related complications (cases) were presented as odds ratios (ORs) for each quintile increase of a given chemical. All models were adjusted for the sample weight and the number of previous pregnancies. Considering its anticipated inverse association with PFAS placental concentrations and potential link to birth complications, adjustment for the number of pregnancies was considered necessary to address any potential confounding effects on the association under study.

We graphically described the PFAS chemicals by study groups using a box plot.

A significance threshold was set to 10 % and aligned with a 90 % confidence interval (CI) presented throughout the analysis. The analysis was performed on SAS 9.4.

3. Results

During the study period, we collected 50 samples of women of Jewish origin who gave birth in the SUMC. The sample comprised 10

women with at least one of the pregnancy-related complication and 40 women without those complications individually matched by age to cases at a 1:4 ratio. The cases included 2 women diagnosed with pre-eclampsia, 7 with GDM, and 1 woman had a newborn diagnosed by SGA. Women were on average (mean±sd) 31.91 ± 5.05 years old (Table 1). All women had term pregnancies, experiencing on average their 3rd delivery. Only one woman (2.0 %) had experienced pregnancy loss, 2 women were obese (4.0 %), 3 had a history of preterm delivery (6.0 %), and 2 were diagnosed with type 2 diabetes (4.0 %). In general, both study groups were healthy, besides the events defining their case status. The average birth weight was 3326 ± 431 g, 46.0 % of newborns were males (23/50), and all newborns had normal Apgar scores at 1st and 5th minute (Table 2).

The PFAS chemicals' distribution is presented in Table 3, by study group and for the entire sample. Eight (8) out of 13 PFAS chemicals were

Table 1
Demographical and clinical characteristics of the study population, by study group.

Subjects' characteristics	Cases (N = 10)	Controls (N = 40)	Total (N = 50)	p-value
<i>Demographical</i>				
Maternal age, years	31.98 ±	31.90 ±	31.91 ±	.481 ^a
Mean± SD (n)	5.34	5.05	5.05	
Median	32.15	32.15	32.15	
Min; Max	24.61; 41.34	24.37; 41.34	24.37; 41.34	
Jewish ethnicity, % (n/N)	100.0 (10/10)	100.0 (40/ 40)	100.0 (50/50)	
Lack of perinatal care, % (n/N)	0 (0/10)	7.5 (3/40)	6.0 (3/ 50)	.372
<i>Clinical background</i>				
Diabetes mellitus, type 2, % (n/ N)	0 (0/10)	5.0 (2/40)	4.0 (2/ 50)	.470
Maternal tobacco use disorder, % (n/N)	0 (0/10)	2.5 (1/40)	2.0 (1/ 50)	.614
Obesity or obesity complicating pregnancy delivery, % (n/N)	0 (0/10)	5.0 (2/40)	4.0 (2/ 50)	.470
Morbid obesity, % (n/N)	0 (0/10)	0 (0/40)	0 (0/50)	—
History of preterm delivery, % (n/N)	0 (0/10)	7.5 (3/40)	6.0 (3/ 50)	.372
Grand multiparity ^b % (n/N)	20.0 (2/ 10)	20.0 (8/40)	20.0 (10/ 50)	1.000
Previous cesarean section, % (n/N)	10.0 (1/ 10)	0 (0/40)	2.0 (1/ 50)	.043
Chronic hypertension, % (n/N)	0 (0/10)	0 (0/40)	0 (0/10)	—
Recurrent pregnancy loss, % (n/N)	0 (0/10)	2.5 (1/40)	2.0 (1/ 50)	.614
<i>Pregnancy characteristics and complications</i>				
Gestational age at birth, weeks	39.86 ±	39.37 ±	39.47 ±	.133
Mean±SD (n)	0.92	1.28	1.22	
Median	39.86	39.36	39.71	
Min; Max	39.00; 42.14	37.00; 41.71	37.00; 42.14	
Gravidity	3.30 ±	3.70 ±	3.62 ±	.703
Mean±SD (n)	2.11	2.36	2.29	
Median	3.50	3.00	3.00	
Min; Max	1.00; 7.00	1.00; 11.00	1.00; 11.00	
Parity	2.70 ±	3.18 ±	3.08 ±	.457
Mean±SD (n)	1.77	2.05	1.99	
Median	2.00	3.00	3.00	
Min; Max	1.0; 6.0	1.0; 11.0	1.0;11.0	
Preeclampsia, % (n/N)	20.0 (2/ 10)	0 (0/40)	4.0 (2/ 50)	— ^c
Gestational diabetes mellitus, % (n/N)	70.0 (7/ 10)	0 (0/40)	14.0 (7/ 50)	— ^c
Oligohydramnios, % (n/N)	10.0 (1/ 10)	5.0 (2/40)	6.0 (3.0)	.279

^a Controls were matched to cases by age. No difference between the study groups is expected.

^b Grand multiparity is defined as 5 or more live or still births at 20 or more weeks of gestation.

^c This diagnosis is a part of "cases" definition.

Table 2

Birth outcomes in the study population, by study group.

Newborns' characteristics	Cases (N = 10)	Controls (N = 40)	Total (N = 50)	p-value
Birth weight, grams	3269.00 ± 386.8	3340.1 ± 444.3	3325.9 ± 430.6	.323
Mean±SD (n)				
Median	3317.5	3242.5	3260.0	
Min; Max	2700.0; 3975.0	2439.0; 4615.0	2430.0; 4615.0	
Male gender, % (n/N)	30.0 (3/10)	50.0 (20/40)	46.0 (23/50)	.256
Apgar score at 1st minute	9.0 ± 0.0	9.0 ± 0.0	9.0 ± 0.0	1.000
Mean±SD (n)	9.0; 9.0	9.0; 9.0	9.0; 9.0	
Median				
Min; Max				
Apgar score at 5th minute	10.0 ± 0	10.0 ± 0	10.0 ± 0	1.000
Mean±SD (n)	10.0; 10.0	10.0; 10.0	10.0; 10.0	
Median				
Min; Max				
SGA, % (n/N)	10.0 (1/10)	—	2.0 (1/50)	— ^a

^a This diagnosis is a part of “cases” definition.

detected in fewer than 10% of women. These included PFBA, PFPeA, PFHxA, PFHpA, PFDoDA, PFUnDA, PFBS and PFHpS. The remaining 5 compounds were further compared between the study groups and against findings in similar studies. The geometric mean was estimated at 0.09 ng/g (90%CI: 0.07; 0.10), for PFOA, 0.05 ng/g for PFNA (90%CI: 0.04; 0.07), 0.03 ng/g for PFDA (90%CI: 0.01; 0.03), 0.06 ng/g for PFHxS (90%CI: 0.05; 0.07) and 0.23 ng/g for PFOS linear measurement (90%CI: 0.20; 0.26). In 7 subjects, non-linear PFOS isomers were detected, resulting in a summed PFOS value of 0.25 ng/g (90%CI: 0.22; 0.30). The cases were likely to have numerically higher values of PFOA, PFNA, PFDA, and PFHxS and only PFOS were lower, as illustrated by the box plot (Fig. 1).

We used median values to compare with concentrations of PFAS presented in other studies from China, Spain, Denmark, Sweden, and USA (Table 4). In this comparison, the PFAS values in the current analysis were consistently lower than the ones reported by other groups.

Analysis adjusting to the matched design, weight of placenta and number of pregnancies, in addition to age-adjustment achieved by matching design, established a significant association between increase

in PFOA quintiles and the likelihood of pregnancy-related complication, with an OR 1.82, 90%CI: 1.06; 3.13 (Fig. 2). A similar, but non-significant finding was recorded for the PFHxS quintiles, with an OR 1.57, 90%CI: 0.94; 2.46. Associations with PFNA and PFDA presented with similar trends but none of these was significant. PFOS chemical measurements appeared to have a protective effect, although at a borderline significance, i.e., OR 0.62 and 0.61 with 90%CI: 0.38; 1.02 and 0.36; 1.03, for PFOS linear and PFOS summed measurements, respectively.

All PFAS compounds, except for PFOS, i.e. PFOA, PFNA, PFDA and PFHxS, were found correlated between each other (Table 1, Supplementary material). The presence of non-linear isomers was negatively correlated with PFDA. Analysis of possible associations of PFAS chemicals with demographical and clinical characteristics of the study population, revealed an adverse association of PFOA with preeclampsia diagnosis (Spearman rho= 0.28, p-value= 0.053, Table 2, supplementary analysis). An advanced gestational age was characterized by increased PFHxS (Spearman rho= 0.27, p-value= 0.060) and lower likelihood of non-linear isomers (Spearman rho= −0.29, p-value= 0.043). Of note, placental PFOA and PFNA were lower in women with higher number of pregnancies and births in the past.

PFAS burden score was calculated using the 7 chemicals measured in our study (instead of the 8 required for the score); however, the resultant values were not associated with any of the parameters investigated in the study (results not shown).

4. Discussion

The present study was aimed at estimating the concentrations of PFAS compounds in placenta in a general population of Jewish women in southern Israel. We found that 5 out of 13 PFAS compounds were above the level of quantification for more than 90% of the study population. Median concentrations were lower or comparable to measurements reported by other researchers worldwide. Older women tended to have higher levels of exposure whereas women with multiple pregnancies had lower levels of exposure, findings which underscore the bio-accumulation of these compounds.

To address our secondary objective, we compared women with or without adverse perinatal outcomes and established an adverse association with higher PFOA concentration, independent of possible confounders.

Table 3

Distribution of PFAS chemicals, by study group.

PFAS chemicals, ng/g	Proportions >LOQ, %			Geometric means, 90%CI ^a			Median; Maximum ^a		
	Cases (N = 10)	Controls (N = 40)	Total (N = 50)	Cases (N = 10)	Controls (N = 40)	Total (N = 50)	Cases (N = 10)	Controls (N = 40)	Total (N = 50)
PFBA	0.0 %	0.0 %	0.0 %	— ²	— ²	— ²	— ²	— ²	— ²
PFPeA	0.0 %	0.0 %	0.0 %	— ²	— ²	— ²	— ²	— ²	— ²
PFHxA	0.0 %	0.0 %	0.0 %	— ²	— ²	— ²	— ²	— ²	— ²
PFHpA	0.0 %	2.5 %	2.0 %	— ²	— ²	— ²	— ²	— ²	— ²
PFOA	70.0 %	55.0 %	58.0 %	0.11 (0.08; 0.16)	0.08 (0.07; 0.10)	0.09 (0.07; 0.10)	0.13; 0.23	0.08; 0.82	0.08; 0.82
PFNA	70.0 %	67.5 %	68.0 %	0.05 (0.04; 0.07)	0.05 (0.04; 0.07)	0.05 (0.04; 0.07)	0.06; 0.13	0.04; 6.52	0.04; 6.52
PFDA	10.0 %	10.0 %	10.0 %	0.03 (0.02; 0.04)	0.02 (0.02; 0.03)	0.03 (0.01; 0.03)	0.03; 0.07	0.02; 0.22	0.02; 0.21
PFDoDA	0.0 %	5.0 %	4.0 %	— ²	— ²	— ²	— ²	— ²	— ²
PFUnDA	0.0 %	10.0 %	8.0 %	— ²	— ²	— ²	— ²	— ²	— ²
PFBS	0.0 %	2.5 %	2.0 %	— ²	— ²	— ²	— ²	— ²	— ²
PFHxS	40.0 %	25.0 %	28.0 %	0.08 (0.06; 0.12)	0.05 (0.05; 0.06)	0.06 (0.05; 0.07)	0.08; 0.26	0.06; 0.21	0.06; 0.26
PFHpS	0.0 %	5.0 %	4.0 %	— ²	— ²	— ²	— ²	— ²	— ²
PFOS linear	100.0 %	100.0 %	100.0 %	0.19 (0.14; 0.27)	0.24 (0.21; 0.28)	0.23 (0.20; 0.26)	0.16; 0.60	0.24; 0.68	0.24; 0.68
PFOS summed	100.0 %	100.0 %	100.0 %	0.19 (0.14; 0.27)	0.27 (0.24; 0.32)	0.25 (0.22; 0.30)	0.16; 0.60	0.28; 0.77	0.26; 0.77

^a Estimates of geometric mean, median and maximal values are reported for chemicals with at least 10% detection in the study sample.

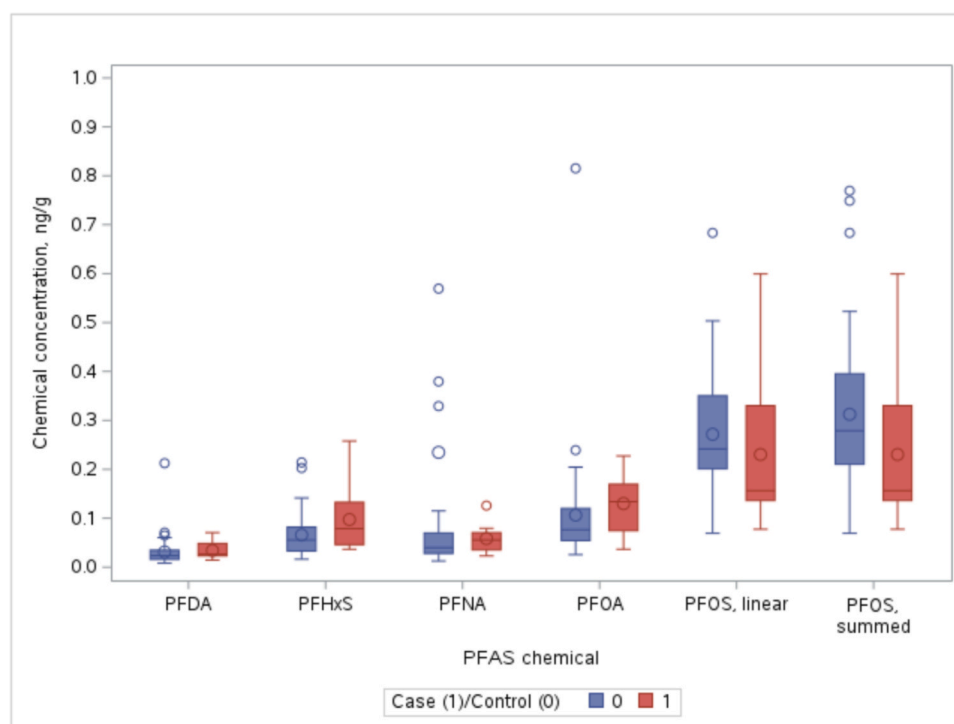


Fig. 1. PFAS chemicals, by study group.

This has been the first study in the country testing PFAS chemicals in placenta, and the second testing these chemicals, in general ([Exposure to PFAS per- and polyfluoroalkyl compounds Among adults in Israel, 2022](#)).

It is notable that the PFAS concentrations in the placenta in our study were consistently lower than those previously reported worldwide. One possible explanation for this could be the later period of our study, which took place mostly in the years 2019–2021, as compared to previously published findings ending in 2018. This decrease may reflect a growing awareness of the potential hazards of PFAS chemicals, leading to stricter regulations worldwide, specifically targeting long-chain compounds ([Bock and Laird, 2022](#)). Alternatively, this may indicate actual variations in exposures between different populations. Another

potential explanation is variations in detection levels or methodology of handling values below the LOQ across the studies. Lastly, it is important to take into account that lower PFAS concentrations could be attributed to the inclusion of exclusively female participants in the sample, as pregnancies and/or breastfeeding in women have the potential to decrease PFAS values.

The findings of PFOA in placenta being an independent risk factor for adverse perinatal outcomes are consistent with current research. In our study, the 10 cases included 7 cases of GDM, 2 cases of preeclampsia, and one woman whose newborn was diagnosed with SGA. With respect to GDM, a meta-analysis of 8 studies has established a positive association between PFOA serum concentration exposure and GDM ([Wang et al., 2022](#)). The OR for the highest quartile of exposure compared to

Table 4

Summary of placenta PFAS concentrations (ng/g) reported in the published literature and the present study (*reprinted from Hall et al (Hall et al., 2022).*).

Reference	Year of Sample collection	Location	Sample size (n)	Value	PFOS	PFOA	PFNA	PFDA	PFHxS
Zhang et al. (2013)	2010	China	n = 29	Median	7.32	1.41	0.96	0.67	0.36
Martin et al. (2016) ^a	Unknown	Spain	n = 25	Range	<LOQ-1.2	<LOQ-0.37	-	-	-
Chen et al. (2017)	2015–2016	China	n = 32	Median	2.42	0.46	-	-	0.21
Mamsen et al. (2017) ^b	2014–2015	Denmark	n = 34	Mean	1.30	0.23	0.14	0.1	-
Mamsen et al. (2019) ^c	2015–2016	Sweden	n = 21	Median	1.42	0.36	0.17	0.24	-
Mamsen et al. (2019) ^d	2014–2016	Sweden & Denmark	n = 78	Median	1.24	0.30	0.15	0.18	-
Bangma et al. (2020)	2015–2018	North Carolina, USA	n = 122	Median	0.48	< 0.32	< 0.16	< 0.03	0.07
Vela-Soria et al. (2021)	Unknown	China	n = 20	Median	0.60	0.14	0.06	0.03	0.07
Lu et al. (2021)	2016	China	n = 54	Median	0.35	0.18	0.06	-	0.08
Hall et al. (2021)	2010–2011	North Carolina, USA	n = 120	Median	0.95	0.27	0.11	0.06	-
Present study (Groisman et al.)	2018–2021	Israel	n = 50	Median	Linear – 0.24 Summed – 0.26	0.08	0.04	0.02	0.06

Blank values were either not reported, below limit of quantification (<LOQ), or <MDL.

^a Ranges reported in lieu of medians because very few samples had quantified concentrations.

^b No median values were reported.

^c Only placentae from third trimester pregnancies are included.

^d Placenta samples from all pregnancies are included.

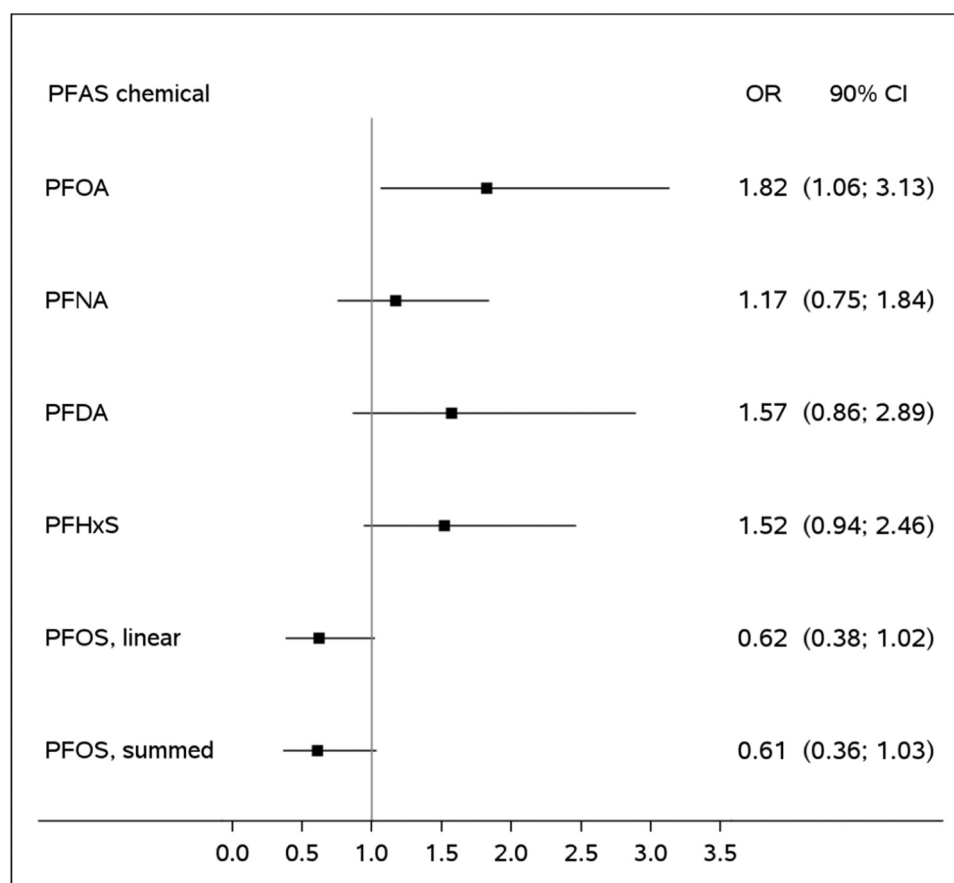


Fig. 2. Associations between the quintiles of PFAS chemicals and pregnancy complications. Results of conditional logistic regression. ¹ The estimates are adjusted for clustered design, weight of placenta samples and number of pregnancies including the index event.

the lowest was estimated at 1.27 (95% CI: 1.02–1.59). As in our study, none of the other PFAS compounds studied have been found associated with diabetes in pregnancy.

Our study is in line with the findings of a recent meta-analysis suggesting a possible relationship between PFOA and preeclampsia. In this report, the researchers found an association with an odds ratio (OR) of 1.18 (95 % confidence interval: 1.01–1.39), although the units of PFOA increase were not specified in the publication (Hirke et al., 2023).

There are several factors to consider when calculating the PFAS burden in placenta samples. In our study, we followed the code provided by Liu et al (Liu et al., 2022), although we were missing data on one of the 8 composites required for the formula. In contrast to analyzing specific PFAS chemicals, where some were observed to be associated with particular outcomes, the combined score did not reveal any meaningful associations in our data. There are several possible reasons for this. One is that we did not have data on one of the 8 elements required for the score. Additionally, many of our concentrations were below the LOQ and therefore imputed with LOQ/sqrt(2) values, which may not have contributed sufficient variation to the PFAS burden score. Finally, the score was designed for PFAS concentrations measured in blood, while placenta tissue measurements may require a different method of integration.

Furthermore, there is a chance that the potential connection between preeclampsia and PFAS levels might be underestimated, as albuminuria presence has been linked with preeclampsia based on an animal model (Ansari et al., 2023), which in turn could result in reduced serum PFAS levels (Jain and Ducatman, 2022, 2019). However, this potential bias could only pull the association towards the null hypothesis, thereby

representing a conservative approach in the analysis.

There are several *limitations* to this study. The most notable limitation is the relatively small sample size, although the number of subjects is comparable to those in other studies investigating the placenta worldwide. Unlike testing blood samples, collecting placenta samples is more invasive and requires careful planning and preparation for enrollment and sample storage, in addition to complex laboratory analysis. Furthermore, as the placenta is a complex organ, in our experimental design we could not evaluate the concentration of PFAS in a specific region of the placenta (e.g., maternal or fetal side).

Another limitation is that the study population does not include the Bedouin-Arab population and therefore does not represent all ethnic groups in Israel. Additional research is required to fully characterize the entire population in the country.

The principal *advantage* of this study is that the sample was taken from a general population of women who were hospitalized for delivery at the sole tertiary hospital providing obstetric services in the region. This ensures that there is no bias in the selection of the population within the stratum of Jewish women, apart from the typical non-compliance rate.

In conclusion, pregnant women in Israel are exposed to several PFAS compounds. The levels of PFAS concentrations in the placenta of pregnant women in southern Israel were relatively low compared to other populations. PFOA concentrations in the placenta appeared to be associated with adverse perinatal outcomes, consistent with findings for PFAS concentrations in blood.

Our findings suggest the need for incorporating PFAS testing as a routine part of human biomonitoring at the national level. As with many

biomarkers of exposure, it is important to prioritize testing in high-risk populations, and to use HBM data to track trends in exposure, characterize sources of exposure, and compare results to HBM guidance values, in order to support policy decisions.

CRedit authorship contribution statement

Luda Groisman: Methodology, Lab analysis, Writing, **Tamar Ber-**
man.: Supervision, Visualization, Writing, **Anna Quinn:** Writing-
Original draft preparation, Investigation, Data analysis. **Gali Pariente:**
Supervision, **Efrat Rorman:** Supervision, Lab analysis, **Isabella Kar-**
akis: Visualization, Reviewing and Editing, **Roni Gat:** Samples collec-
tion, Lab analysis, **Batia Sarov:** Conceptualization, Review, **Lena**
Novack: Conceptualization, Data Analysis, Writing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ecoenv.2023.115165](https://doi.org/10.1016/j.ecoenv.2023.115165).

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