

PFAS and Maternal reproductive outcomes: Associations with Miscarriage and Preeclampsia

Collaborative on Health and the Environment:
Generation Chemical webinar

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Disclosures

Conflict of interest

- None. The studies received grants from the Swedish Research Council for Environment, Agricultural Sciences and Spatial Planning, and the County Council of Värmland, Sweden.

Human rights

- The studies were performed in accordance with the Declaration of Helsinki.
- The Regional Ethical Review Board in Uppsala, Sweden approved the study protocols.
- Written informed consent was obtained from each participating woman.

Expertise

- I am not an OB/GYN specialist (consultant in pediatrics and child/adolescent psychiatry).
- Experience in perinatology.

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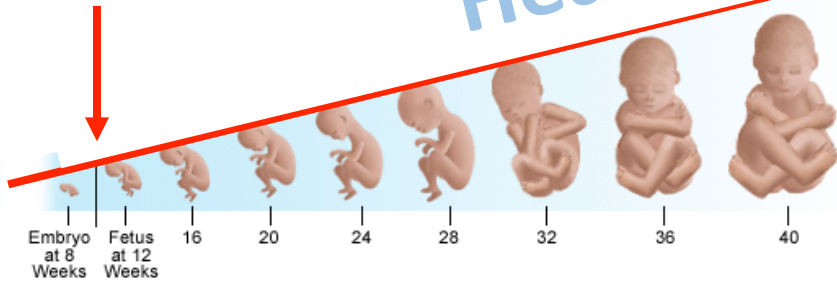
Research for a **healthier** future
Swedish Environmental Longitudinal, Mother and child, Asthma and allergy study



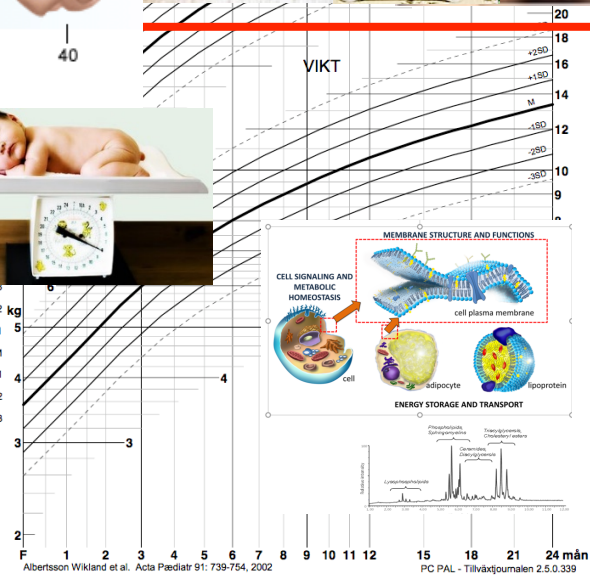
Research for a healthier future

Swedish Environmental Longitudinal, Mother and child, Asthma and allergy study

54 EDCs
(N=+2,300 women)
Single Compounds & Mixtures



Health and development

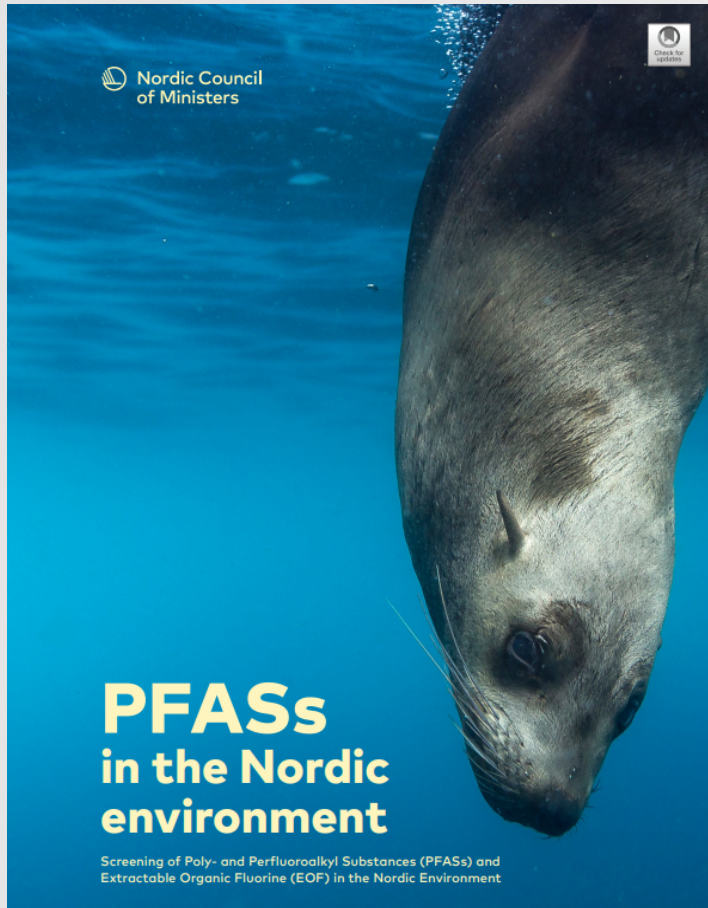


Per- and polyfluoroalkyl substances

- Hydrophobic and oleophobic.
- In food contact materials, electronic industry, production of plastics and rubber, cosmetics, lubricants and grease, polish, ski wax, waterproof clothing, stain resistant fabrics, non-stick materials, fire fighting foams.
- Very persistent “Forever Chemicals”. Difficult to reduce exposure.
- Will accumulate.
- Long half-life in human.



Everyone is exposed to PFAS, primarily via diet (e.g. seafood)



PFAS levels in the SELMA study: Low level community exposure

Table 2. Prenatal exposure to eight PFAS, measured as maternal serum concentrations (ng/mL) during early pregnancy.

Compound	Geometric mean [95% CI]	Median (IQR)	95th %	LOD	Above LOD (%)
PFOS	5.35 [5.21–5.50]	5.38 (3.97–7.60)	10.34	0.06	100
PFOA	1.60 [1.56–1.65]	1.61 (1.11–2.30)	3.18	0.02	100
PFHxS	1.31 [1.28–1.35]	1.23 (0.86–1.99)	2.94	0.03	100
PFNA	0.54 [0.53–0.56]	0.53 (0.39–0.73)	1.02	0.01	100
PFDA	0.26 [0.26–0.27]	0.26 (0.19–0.34)	0.50	0.02	100
PFUnDA	0.21 [0.21–0.22]	0.23 (0.15–0.33)	0.44	0.02	99.5
PFHpA	0.018 [0.017–0.019]	0.02 (<LOD–0.04)	0.077	0.01	73.9
PFDoDA	0.027 [0.026–0.027]	<LOD (<LOD–0.05)	0.08	0.03	46.7

LOD limit of detection

Blood samples at median 10 wks gestational age.

Associations between PFAS exposure and preeclampsia

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Early pregnancy serum levels of perfluoroalkyl substances and risk of preeclampsia in Swedish women

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Preeclampsia is a major cause of maternal and fetal morbidity. Emerging research shows an association with environmental exposures. The present aim was to investigate associations between early pregnancy serum levels of perfluoroalkyl substances (PFAS) and preeclampsia. Within the Swedish SELMA study, eight PFAS were measured at median 10 gestational weeks and cases of preeclampsia were postnatally identified from registers. Associations between individual PFAS and preeclampsia were assessed, adjusting for parity, age, weight and smoking. Out of 1,773 women in the study group, 64 (3.6%), developed preeclampsia. A doubling of PFOS and PFNA exposure, corresponding to an inter-quartile increase, was associated with an increased risk for preeclampsia of about 38–53% respectively. Serum PFOS within the highest quartile was associated with an odds ratio of 2.68 (CI 95%: 1.17–6.12), equal to the increased risk associated with nulliparity, when compared to exposure in the first quartile. The same associations were identified, although with higher risk estimates, in analyses restricted to nulliparous women. For other PFAS, there were no associations. In conclusion and consistent with limited previous research only on PFOS, increasing serum levels of PFOS and PFNA during early pregnancy were associated with a clinically relevant risk of preeclampsia, adjusting for established confounders.

Preeclampsia

- A disorder during the second half of pregnancy.
- Defined by hypertension and proteinuria.
- Headache, nausea, blurred vision, abdominal pain, oedema.



Aim

To investigate associations between early prenatal serum levels of eight individual PFAS and preeclampsia during the same pregnancy.

Why did we study associations between PFAS exposure and preeclampsia?

Plausible association

- Known association with other environmental exposures (air pollution, POPs)
- The “disease of theories”, multiple etiologies are proposed.
 - Abnormal placental implantation Oxidative stress
 - Metabolic disturbances Inflammatory mechanism
- Known factors explain only a small portion of preeclampsia cases. Important to find new risk factors!
- Association between PFAS and birth weight (possibly placenta related).
- PFAS influences the immune system and oxidative stress.

Why did we study associations between PFAS exposure and preeclampsia?

Important threat to maternal health

- Affects 2–8% of pregnancies.
- Major cause of maternal and fetal morbidity.
- Worldwide responsible for more than 10% of maternal mortality.
- Increases long term risk for cardiovascular disease.
- Consequences to the fetus include increased mortality rates, intrauterine growth restriction, preterm birth and developmental impairments.

Method: Study embedded in SELMA

- PFAS analysed in serum samples from 10 weeks of gestation (median)
- Maternal diagnoses collected from the Swedish Medical Birth Register
- Blood pressure and urinary albumin routinely measured at each visit in the free nation-wide antenatal care
- Preeclampsia was diagnosed according to ICD10
 - systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg
 - accompanied by proteinuria (after 20 pregnancy weeks).
- Compound by compound analysis
- Analyses adjusted for parity, age, weight and smoking

Results

- N=1,773 women in the study group of which N=64 (3.6%), developed preeclampsia.
- A doubling of PFOS and PFNA exposure, corresponding to an inter-quartile increase, was associated with an increased risk for preeclampsia of about 40-50 % respectively.
- What about PFOA? Indications according to crude analysis and for the highest quartile of exposure.
- Serum PFOS within the highest quartile was associated with an odds ratio of 2.68 (CI 95%: 1.17–6.12) as compared with first quartile.
- Higher risk estimates in analyses restricted to primiparous women.
- No significant findings for the other four assessed PFAS.

Results

Compound	Crude OR (95% CI)	Adjusted ^a OR (95% CI)
(a) All women (n = 64 cases of preeclampsia)		
PFOS	1.74 [1.23–2.46]	1.53 [1.07–2.20]
PFOA	1.53 [1.13–2.07]	1.31 [0.93–1.87]
PFHxS	1.21 [0.91–1.62]	1.16 [0.86–1.56]
PFNA	1.50 [1.11–2.01]	1.38 [1.01–1.89]
PFDA	1.19 [0.85–1.66]	1.11 [0.79–1.59]
PFUnDA	0.93 [0.72–1.21]	0.89 [0.68–1.17]
PFHpA	1.04 [0.88–1.23]	1.02 [0.86–1.21]
(b) Nulliparous women (n = 42 cases of preeclampsia)		
PFOS	2.06 [1.29–3.39]	2.02 [1.26–3.29]
PFOA	1.36 [0.89–2.17]	1.38 [0.90–2.21]
PFHxS	1.23 [0.84–1.78]	1.24 [0.85–1.82]
PFNA	1.44 [1.01–2.06]	1.50 [1.04–2.16]
PFDA	1.24 [0.83–1.84]	1.29 [0.86–1.96]
PFUnDA	1.00 [0.72–1.41]	0.99 [0.69–1.42]
PFHpA	0.99 [0.81–1.21]	1.00 [0.82–1.22]

Odds Ratios per one unit increase in log base-2
PFAS level (i.e doubling of exposure)

Conclusions

- Higher serum levels of PFOS, PFNA (and PFOA) at 10 weeks of gestation were associated with preeclampsia.
- Importantly, risk estimates were highest among primiparous women.
- PFOS levels in the fourth quartile of exposure were, as compared with first quartile, related to an odds ratio for preeclampsia of the same size as for primiparity (a well-established and major risk factor).

Associations between PFAS exposure and miscarriage (pregnancy loss <20wks)

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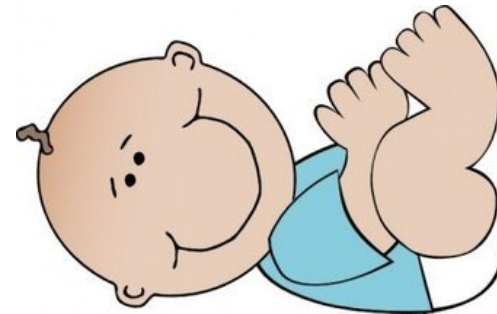
OPEN Exposure to perfluoroalkyl substances in early pregnancy and risk of sporadic first trimester miscarriage

Sverre Wikström¹✉, Ghada Hussein^{2,3}, Annika Lingroth Karlsson¹, Christian H. Lindh⁴ & Carl-Gustaf Bornehag^{5,6}

Many first trimester sporadic miscarriages are unexplained and the role of environmental exposures is unknown. The present aim was to study if levels of Perfluoroalkyl substances (PFASs) in early pregnancy are associated with unexplained, sporadic first trimester miscarriage. The study was performed within the Swedish SELMA pregnancy cohort. Seventy-eight women with non-recurrent first trimester miscarriage were included and 1449 women were available as live birth controls. Eight PFASs were measured in first trimester serum. A doubling of perfluorooctanoic acid (PFOA) exposure, corresponding to an inter-quartile increase, was associated with an odds ratio (95%CI) for miscarriage of 1.48 (1.09–2.01) when adjusting for parity, age and smoking. Analyses per quartiles of PFOA exposure indicated a monotonic dose response association with miscarriage. A similar, but not significant, pattern was observed for perfluorononanoic acid (PFNA). For other PFAS, there were no associations with miscarriage. We have previously shown associations between early pregnancy PFAS exposures and preeclampsia, as well as lower birth weight. Now we report an association between PFOA and miscarriage within the same cohort, which may suggest shared but unknown mechanisms.

Aim

To investigate whether maternal exposure to PFAS in early pregnancy is associated with unexplained, sporadic first trimester miscarriage of the same pregnancy.



"Overall aim"

Why did we study associations between PFAS exposure and first trimester miscarriage?

Plausible association

- Multifactorial background (genetic, advanced maternal age, endocrine or immunological dysregulation, lifestyle including smoking, etc). A large number of first trimester sporadic miscarriages are unexplained!
- Miscarriage, preeclampsia and reduced fetal growth share a relation to placental dysfunction.
- Experimental support for effects from PFAS on placentation.

Clinical importance

- Miscarriage is common, ends 10-20% of identified pregnancies.
- About 80% occur during first trimester.
- Physical and emotional suffering.

Method: Study embedded in SELMA

- Blood samples by study recruitment.
- Excluded all women previously having more than three consecutive pregnancy losses or kidney disease, and miscarriages obviously explained by pre-defined maternal or fetal conditions.
- Miscarriages before 12 weeks+6 days of pregnancy.
- Adjusted for age of the mother, parity and tobacco smoke exposure during pregnancy.

Results

N=78 women with sporadic, unexplained miscarriage during second half of first trimester.
N=1449 live birth controls.

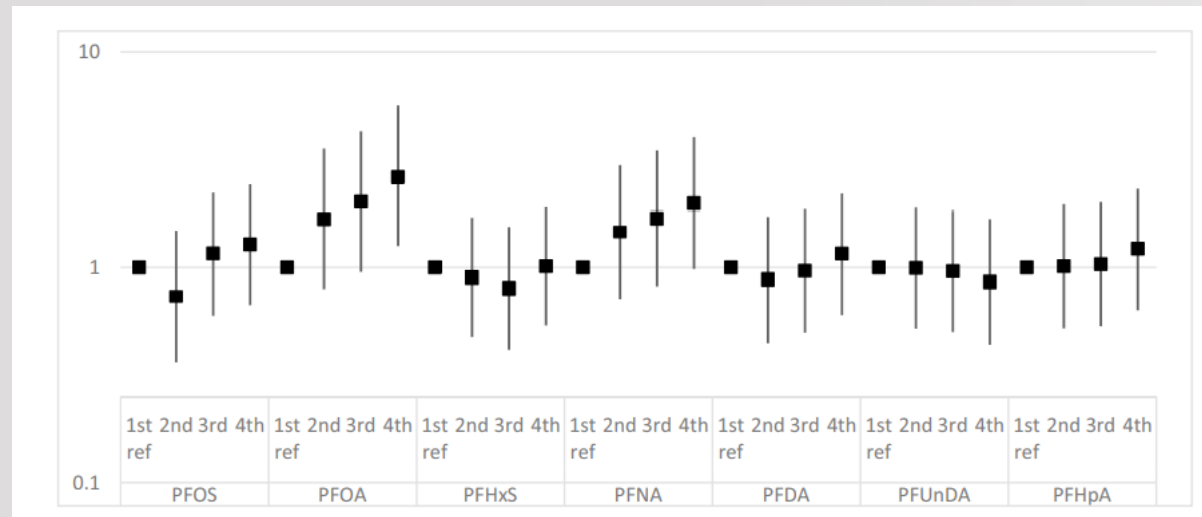
Compound	Crude OR (95% CI)	Adjusted ^a OR (95%CI)
PFOS	1.13 (0.84–1.53)	1.13 (0.82–1.52)
PFOA	1.38 (1.04–1.83)*	1.48 (1.09–2.01)*
PFHxS	0.96 (0.73–1.26)	0.96 (0.73–1.26)
PFNA	1.25 (0.94–1.66)	1.25 (0.93–1.68)
PFDA	1.14 (0.84–1.55)	1.10 (0.81–1.53)
PFUnDA	1.00 (0.78–1.28)	0.95 (0.74–1.22)
PFHpA	1.09 (0.93–1.27)	1.09 (0.93–1.28)

Odds Ratios per one unit increase in log base-2 PFAS level (i.e doubling of exposure)

For PFOA, a doubling of exposure, corresponding to an increase from 25:th to 75:th percentile of exposure, was associated with an OR(95%CI) for miscarriage of 1.48 (1.09–2.01).

Results

Adjusted associations between PFAS and miscarriage, presented by quartiles of exposure with respectively first quartile exposure as reference.



Conclusions

- We now add an association between first trimester PFOA levels and increased risk for sporadic miscarriage during the second half of the first trimester to the associations with preeclampsia as well as lower birth weight already shown in the SELMA cohort.
- The present study may only represent sporadic clinical miscarriages during a period of early placentation.
- The emerging indications of PFAS effects on human reproduction outcomes suggest shared mechanisms. Miscarriage, preeclampsia and impaired fetal growth share in common the association with abnormal placentation and placental oxidative stress.



**Collaborative on
Health and the
Environment**

Thank You all for listening!

If You did not attend them, I recommend the recorded previous webinars by Collaborative on Health and the Environment, on PFAS, Science and Policy (Dr Rainer Lohmann, Dr Ian Cousins, Dr Xenia Trier). I learned a lot from them!

Preeclampsia:

How our findings relate to other studies

- Savitz et al. (C8 Health Project): An increase from the 25th to the 75th percentile in PFOA exposure was associated with an OR of 1.13[95% CI: 1.0–1.6] for preeclampsia.
- Stein et al. (C8 Health Project): OR of 1.3[95% CI: 0.9–1.9] for preeclampsia in women with PFOA levels above as compared to below the mean, and similar an OR of 1.3[95% CI: 1.1–1.7] for PFOS levels above vs below mean
- Starling et al. (Norwegian MoBa cohort): Increased levels of PFOS and PFHpS had minor associations with preeclampsia risk (Hazard Ratio=1.13[95% CI: 0.84–1.52] per ln-unit increase in PFOS) while PFNA exposure showed no association with preeclampsia.
- Borghese et al. (MIREC study): Higher levels of PFHxS were associated with preeclampsia (but not PFOA or PFOS) Fetal sex modified these associations.
- Rylander et al. (Southern Sweden Maternal Biobank): Among primiparous women, there were no differences in PFAS between cases and controls. In multipara women, cases had higher PFNA.
- Huang et al. (Shanghai): Perfluorobutane sulfonate (PFBS), PFHxS and perfluoroundecanoic acid (PFUA) were associated with preeclampsia PFAS.

Miscarriage:

How our findings relate to other studies

- Liew et al. (Danish National Birth Cohort): Association between maternal PFOA and second trimester miscarriage (n = 220 cases). Strongest among parous women. OR(95%CI) for miscarriage with a doubling of PFOA exposure= 1.4 (1.0–1.9), as compared with 1.48 (1.09–2.01) in the present study. The Danish study reported an OR in the highest quartile of PFOA exposure of 2.2(95% CI: 1.2- 3.9) and the corresponding OR in our study was 2.66 (1.26–5.65).
- Other studies on PFAS exposure in relation to miscarriage identified no associations for PFOA.
- Darrow et al. (C8 Health Project): Modest association between PFOS and miscarriage in a sub group analysis. Not replicated in our study.
- Jensen et al. (Odense, Denmark): Marked increase in risk for miscarriage with increasing PFNA, odds ratio of 16.17(95%CI: 6.88–38.03) for women in the highest tertile of exposure as compared with lowest tertile. Also PFDA was there associated with miscarriage.
- Louis et al. (LIFE study): Pregnancy loss risk reduction with Hazard Ratio (95%CI) 0.57(0.34–0.94) at PFNA exposures in the third versus first tertile.

Preeclampsia: Differences between studies

- Medical Birth Registry reports by health care professionals, the authors from the *C8 Health Project* (investigating questionnaire self-reports of preeclampsia)
- Sample size
- indirect measures (PFAS model estimates or inclusion of pregnancies five years preceding serum measurements in the *C8 Health Project* reports), mid-pregnancy serum measurements (*MoBa*), and early pregnancy serum
- Exposure levels: Live birth bias?

Miscarriage: Differences between studies

- Exposure levels: Blunting of threshold effects present already at lower exposure levels? Association between PFOA exposure and reduced fertility?
- Sample size
- First trimester/second half of first trimester/second trimester/ before 20wks
- Inclusion criteria: Clinical miscarriage? Unexplained? Sporadic vs recurrent?

Preeclampsia: Confounders?

- History of preeclampsia and heredity
- Pre-pregnancy renal dysfunction
- Changes in Glomerular Filtration Rate (GFR), plasma expansion and serum albumin changes during pregnancy
- Additional and unmeasured environmental exposures

Miscarriage: Confounders?

- Age
- Tobacco smoke exposure
- Parity
- Inter pregnancy interval
- Glomerular filtration rate (GFR)
- Timing of blood sampling
- Time of fetal death
- BMI
- Education, SES