



Perfluoroalkyl substances and metabolic outcomes in pregnancy

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Comment on: Matilla-Santander N, Valvi D, Lopez-Espinosa MJ, *et al.* Exposure to Perfluoroalkyl Substances and Metabolic Outcomes in Pregnant Women: Evidence from the Spanish INMA Birth Cohorts. *Environ Health Perspect* 2017;125:117004.

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Perfluoroalkyl substances (PFASs) were put on the market more than 50 years ago. They were not believed to enter biological systems or to be biologically active and it came as a big surprise when they were found in wildlife. Later, they were found in humans and are now ubiquitously present in many populations. It is of concern but we still do not know how serious the potential health problems are.

About 10 years ago, PFASs could only be measured in a few laboratories worldwide and only perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS). Now, more types of PFASs are measurable in numerous laboratories. Many believed that low concentrations of PFASs would not cause any harm. Others had a different view. Studies in rodents, which were soon conducted on human data too, showed PFAS exposures to be related to low birth weight (1). No human studies have had data to evaluate fetal growth but a low birth weight according to gestational age at birth indicates fetal growth impairment, and possibly a “fetal programming” effect on health and diseases later in life. It was hypothesized that the fetuses would use the time period of fetal life to adapt to the expected external environment. For instance, if the external environment did not provide enough energy to sustain normal growth, the fetus could benefit from a mechanism that would allow storage of fat and other metabolic changes to provide energy in periods of energy shortage. Many observations do not contradict these speculations and in fact this theory received further support when research demonstrated that epigenetic changes could be induced by environmental exposures, including PFASs (2), present in the period of fetal development.

Both animal and human studies suggested that PFAS levels correlate with se-cholesterol and that epigenetic changes modify the gene expression that could be of importance. However, a correlation is not necessarily a causation—but it could be. In any case, epigenetic modulation probably is part of the mechanism that we consider “fetal programming” effects or fetal origin of health and diseases later in life.

The study by Matilla-Santander *et al.* is, however, not addressing fetal programming but metabolic alterations in the mother; impaired glucose intolerance, gestational diabetes (GDM) and serum levels of triglycerides, cholesterol and C-reactive protein. They used data from an existing birth cohort with rather broad aims. The original cohort included about 2,150 pregnant women early in pregnancy; PFAS levels were measured in about half of them who had available pregnancy plasma samples and were followed for four years after birth. Given this information, they could analyze maternal metabolic markers as a function of the mother’s exposure to PFASs. The analysis was carefully conducted. However, several exposure and outcome markers were analyzed, and without a specific and a priori well-defined hypothesis, results are difficult to interpret. We do not know if separate PFAS exposures should be analyzed in a combined exposure index, or be analyzed, as the authors do, as separate exposures that perhaps even need to be adjusted by other PFAS exposures. We have limited information available to justify a specific strategy for confounder adjustments. We do not know which variables should be in a confounder score or in a propensity score. We know that PFAS exposures correlate with

some food items, socioeconomic status and occupational factors (3), but we do not know enough to provide a strong case for valid confounder control.

A pregnancy order (sibling like) design would be an option if PFAS exposures would vary largely for reasons not related to anything else than the external exposures. By using this design—comparing outcomes in one pregnancy with those of another pregnancy—women become their own controls and proper conditional analyses should adjust for all time stable confounders, a strong requirement if metabolic disorders are to be followed over post-partum observation time and we expect the exposure contrast to be limited in pregnancy pairs.

If internal PFAS exposure levels would be strongly influenced by genetic factors, a Mendelian randomization study could be an option given these genes having no pleiotropic effects—that they only influence interval exposure levels. These genes would then serve as an instrumental proxy variable for the PFAS exposures and remove confounding by causal paths starting at the exposure and ending at the outcome.

None of these designs appear to be very attractive, but the only good alternative, a randomized control trial, can only be done in animal studies.

Information bias is also of concern—many of the outcome data address a short time period open for data collection. Validity of routine clinical measures such as GDM may be low and random measurement error of both exposures and outcome could produce substantial bias—most likely towards the null. Reverse causality should also be discussed; is it possible that women with metabolic dysfunctions over the years were likely to accumulate higher levels of these chemicals with long half-lives from their diets and the living environment?

Ecological studies should not be dismissed. PFAS exposures vary over time and between populations and if exposure levels do not in any way correlate with the outcome by time or space then we have reason to be less concerned. PFAS exposures have, for example, been considered a potentially strong obesogenic factor (4) but if the obesity epidemic has no correlation with PFAS levels in the population over time, we probably should start looking

for other causes.

We need more research which unfortunately is not just a routine statement as seen in many research reports. We still have limited follow-up time from most of the cohorts to study long-term effects of PFAS exposures. Some studies have shown a correlation between PFAS exposures and waiting time to pregnancy (5), and the potential effect on fetal growth is also quite well documented. We may, however, see other effects after 10 to 40 years of induction and latency time.

Time will show—hopefully, it will not be too late.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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