

## PFAS and Miscarriage in Humans: Expanding a Sparse Evidence Base

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Studies have linked certain per- and polyfluoroalkyl substances (PFAS) to adverse birth outcomes in rodents, such as pregnancy loss, reduced growth, and pup death.<sup>1,2</sup> In humans, there is some evidence of an association with pregnancy-induced hypertension,<sup>3</sup> lower birth weight,<sup>3</sup> and miscarriage.<sup>4</sup> Now a nested case–control study published in *Environmental Health Perspectives* further assesses whether PFAS exposure is associated with miscarriage risk in humans.<sup>5</sup>

The authors of the new study examined the relationship between exposure to seven PFAS and miscarriage risk in women recruited in 1996–2002 for the Danish National Birth Cohort. Study participants included random samples of 220 women who had miscarriages and 218 women who gave birth. Lead author Zeyan Liew, an assistant professor of environmental health sciences at Yale University’s School of Public Health, notes that the exposure level for PFAS were comparable between Denmark and the United States during the 1996–2002 study period.

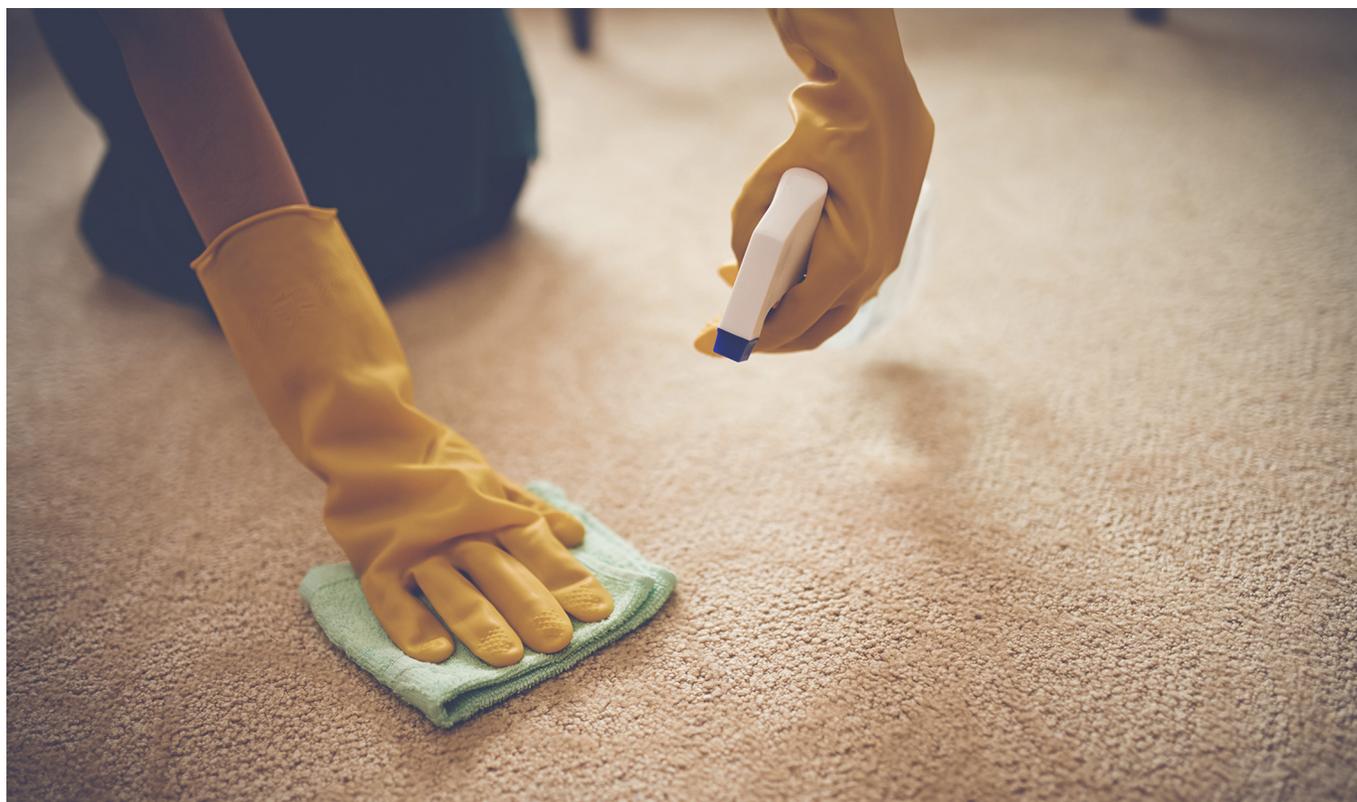
The investigators tested blood samples provided around gestational week 8 for seven PFAS: perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), perfluorohexane sulfonate (PFHxS), perfluoroheptane sulfonate (PFHpS), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), and

perfluorooctanesulfonic acid (PFOSA). Some of these PFAS are newer chemicals being used as replacements for PFOA and PFOS.

After controlling for confounding factors (maternal age, parity, smoking and alcohol intake during the first trimester, and history of miscarriage, as well as both parents’ socio-occupational status), the authors found that PFOA and PFHpS were most consistently associated with miscarriage. For three other chemicals—PFOS, PFHxS, and PFOSA—the estimated risk of miscarriage was higher for certain quartiles of exposure but with no clear or consistent exposure–outcome pattern. Miscarriage was also associated with an index representing the mixture of all seven PFAS.

“Overall, this is a very well-conducted study and adds a meaningful piece of evidence on the potential effects of PFAS on pregnancy loss and potentially on other pregnancy outcomes as well,” says Youssef Oulhote, an assistant professor of epidemiology at the University of Massachusetts Amherst, who was not involved in the research. “One of the main strengths is this early measurement of PFAS in addition to the reliance on one of the well-characterized birth cohorts.”

Oulhote adds that the authors considered a wide set of confounders and investigated multiple scenarios with a thorough set of sensitivity analyses. “The authors tried to adjust for multiple



PFAS are persistent environmental chemicals found in stain-repellent and nonstick coatings, paints, cleaning products, and many consumer products. Since the early to mid-2000s, production of two widely known PFAS—PFOA and PFOS—has been voluntarily phased out in the United States, and use has been restricted in the European Union.<sup>8</sup> However, these chemicals are being replaced with related compounds for which less is known about potential health effects.<sup>9</sup> Image: © iStockphoto/DragonImages.

risk factors of pregnancy loss and reproductive history,” he says, “but residual confounding cannot be excluded.”

Confounding by parity is perhaps the biggest issue in studies such as this. In one study, expectant women who had previously given birth showed associations between PFAS exposure and time to pregnancy more consistently than women who had not given birth.<sup>6</sup> “Although the last pregnancy outcome and time gap since last pregnancy was controlled for in analyses, the effect estimates seemed to be stronger in parous women,” explains Liew, “which raised concerns of possible residual confounding from women’s reproductive history.”

Tracey Woodruff, director of the Program on Reproductive Health and the Environment at the University of California, San Francisco, found the study interesting. “The Danish National Birth Cohort is a rich and well-constructed source of prospective data for answering questions about environmental exposures and adverse pregnancy outcomes,” says Woodruff, who was not involved in the study. “As the authors note, there are a couple of studies<sup>1,2</sup> finding an association with PFOA and pregnancy loss where PFOA exposure is measured in blood samples. And these studies are supported by more extensive data in animal studies. We should be using animal data more robustly to assess the environmental contribution to miscarriage.”

“Bottom line, we know these chemicals are toxic,” says Woodruff. “We have seen their toxicity in numerous studies of other end points. So from that perspective, this is an important study that adds additional findings indicating that there is an environmental contaminant contribution to this problem. And given that most people in the U.S. are exposed to PFAS,<sup>7</sup> additional support for efforts to mitigate these exposures at the state and federal level is needed.”

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