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Serum perfluoroalkyl acids and time to pregnancy in nulliparous women

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ABSTRACT

Background: Previous studies on the exposure to perfluoroalkyl acids (PFAAs) and female fertility have provided conflicting results. We aimed to investigate the association between several PFAAs and time to pregnancy among nulliparous women.

Methods: From 2008 to 2013, we included 1372 women from the Aarhus Birth Cohort, Aarhus University Hospital, Denmark, who provided data on time to pregnancy and a blood sample before 20 gestational weeks. We measured the levels of 16 PFAAs in maternal serum and report data for seven compounds with quantifiable values in at least 50% of samples. Fecundability ratios according to PFAA levels (quartiles or continuous levels) were estimated by discrete-time survival analyses, adjusted for potential confounders. We further investigated the association between PFAAs and infertility (time to pregnancy > 12 months or infertility treatment prior to the studied pregnancy) by multivariable logistic regression.

Results: Median levels of perfluorooctane sulfonate and perfluorooctanoate were 8.3 and 2.0 ng/mL. Overall, no obvious associations were found between any PFAAs and fecundability or infertility. Adjusted fecundability ratios (95% confidence intervals) were 1.09 (0.92–1.29) for perfluorooctane sulfonate and 1.10 (0.93–1.30) for perfluorooctanoate (highest versus lowest quartile).

Conclusions: We found no evidence of an association between present serum levels of PFAAs and longer time to pregnancy or infertility in nulliparous women. This study further adds to the sparse knowledge on PFAAs besides perfluorooctane sulfonate and perfluorooctanoate.

1. Introduction

Perfluoroalkyl acids (PFAAs) are found in various products due to their unique water-, oil, and stain-repelling properties. They have been used since the 1950s, but the most widely applied compounds [perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA)] have been regulated from the year 2000 and onwards in some countries. In general, PFAAs are environmentally persistent and have yearlong half-lives in humans (Butenhoff et al., 2006; Olsen et al., 2007).

The widespread exposure to PFAAs and their potential to disrupt endocrine functions (Benninghoff et al., 2011; Henry and Fair, 2013; Kjeldsen and Bonefeld-Jørgensen, 2013) have caused concern regarding potential health effects. Some earlier studies investigated the association between the exposure to PFAAs, mainly PFOS and PFOA, and female fecundability measured by the time to pregnancy (TTP) and found conflicting results. When studying this topic it remains controversial whether the analyses should be conditioned on parity. Some researchers have suggested that parity may be an intermediate between the exposure and outcome or a collider (Vélez et al., 2015), but they may not have fully

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considered the time varying causal structures. Considering the timely order, nulliparity per se must precede the PFAA levels at the relevant time of the exposure, and hence nulliparity cannot be considered an intermediate factor between the exposure and the outcome (see Supplementary Fig. S1 in appendix). Since the levels of PFAAs decrease in maternal blood during pregnancy and the breastfeeding period (Glynn et al., 2012), PFAA levels are not constant in the individual women during the relevant exposure windows related to successive pregnancies. In accordance with this parous women generally tend to have lower PFAA levels (Berg et al. 2014; Brantsæter et al. 2013). Careful consideration is needed when exposures are time-varying (Howards et al., 2012). If parous women are studied, exposure levels before the previous pregnancy should be considered. If such information is not available (which it seldom is), we consider it necessary to only study nulliparous women in order to eliminate the risk of reverse causality among parous women (Olsen et al., 2009; Vestergaard et al., 2012; Whitworth et al., 2012) as well as confounding by factors related to previous pregnancies and childbirths, in particular when the setting is a birth cohort. After the levels of PFAAs have decreased in maternal blood during pregnancy, childbirth and lactation, continuous exposure to PFAAs may cause increasing concentrations in parous women. This increase may be proportional with the TTP, and therefore a spurious association may appear if PFAAs are measured around the time of conception instead of when couples started to try to become pregnant. Thus, we restricted our study to nulliparous women.

We aimed to investigate the association between the most abundant PFAAs and time to pregnancy as well as infertility in a recent sample of Danish women. The current study provides the largest sample of nulliparous women investigated to date regarding this association.

2. Materials and methods

2.1. Setting

The Aarhus Birth Cohort (ABC) was founded in 1989 and still collects information on pregnant women, who plan to give birth at the Department of Obstetrics and Gynecology, Aarhus University Hospital, Denmark. Information on the women's life style, obstetric and medical history is collected by self-administered questionnaires completed during pregnancy (Larsen et al., 2013). In 2008, a biobank with blood samples from pregnant women and their partners was added to the cohort. Processing of blood samples is completed within 2 h, and samples are stored in freezers at −80 °C until further analysis. All ABC participants provide written consent (Mortensen et al., 2013). Attending midwives register information about the birth immediately after delivery using a structured form, and until January 2013, data was validated by research midwives.

2.2. Participants

Women included in the cohort during 2008–2013 were eligible if they were nulliparous, planned or partly planned their pregnancy, donated a blood sample between 9 and 20 completed gestational weeks, and gave birth to a live born, singleton neonate. For this study, we included a random sample of 1386 women who fulfilled the criteria. Of these, 1372 women (99%) had complete information on exposures, outcomes, and covariates and were included in the analyses.

2.3. Ethical approval

The Danish Data protection Agency (Reference 2012-41-1288) and the Danish National Committee on Health Research Ethics (Reference M-20110054) approved the project, which was carried out in accordance with the Declaration of Helsinki.

2.4. Exposure assessment

At the Department of Environmental Science, Aarhus University, we measured the levels of 16 PFAAs in maternal serum by high performance liquid chromatography-tandem mass spectrometry after solid phase extraction (Liew et al., 2014). The laboratory staff was blinded to the outcomes under study. The laboratory participates in an ongoing method performance test, the Arctic Monitoring and Assessment Programme (AMAP) Ring Test for Organic Pollutants in Human Serum (organized by Institut National de Santé Publique du Québec). Intra-day and inter-day precision are shown in Supplementary Table S1 (Appendix).

2.5. Outcomes

Information on the planning of the pregnancy, TTP (in months and years), as well as infertility treatment was provided in the prenatally obtained questionnaires, for most participants around 12 gestational weeks. Infertility was defined as a TTP longer than 12 months or infertility treatment before the current pregnancy.

2.6. Statistical analyses

2.6.1. Main analyses

In our analyses, we included PFAAs for which at least 50% of the samples had values above the quantification limit (see Table 1). PFAA values below the limit of quantification (LOQ) were substituted by the LOQ divided by two. The participants were categorized into four groups according to their PFAA levels. The women with exposure levels in the lowest quartile were used as the reference group. Furthermore, the continuous exposure concentrations were rescaled to assess the difference in outcomes per 0.1 ng/mL increase in the levels of the individual PFAAs.

Discrete-time survival models with complementary log–log links were applied to estimate fecundability ratios (FRs). This measure reflects the probability of conceiving during a given cycle, given that the women did not conceive in the previous cycles, comparing women in each of the upper three exposure quartiles to the reference group in the analyses using categorical exposure measures. Likewise, in the analyses using continuous exposure measures, outcomes were compared with respect to a 0.1 ng/mL difference between exposure levels. We censored TTPs above 12 months. Women, who received infertility treatment, were added to the censored group, independently of any reported TTP. The TTP in these women cannot be compared with a spontaneous TTP among women, who did not receive infertility treatment, since their treatment most likely affected the TTP. When using the TTP as a measure of the fecundability, most of these women would belong to the group that is clinically defined as infertile. Further, women receiving infertility treatment may, instead of the TTP, report the time from initiating to try to become pregnant to starting infertility treatment, or the time from starting infertility treatment to conceiving. In addition to FRs, we estimated infertility odds ratios by multivariable logistic regression analyses.

Causal directed acyclic graphs (see Supplementary Fig. S2 in appendix) were used to determine which covariates to adjust for. These included maternal age at delivery (continuous), pre-pregnancy body mass index (BMI, continuous), and maternal level of education (categories: 1. Municipal primary and lower secondary