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Lactation history, serum concentrations of persistent organic pollutants, and maternal risk of diabetes

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ABSTRACT

Objective: Lactation may help curb diabetes risk and is also known as an excretion route for some environmental pollutants. We evaluated associations of lifetime lactation history with serum concentrations of persistent organic pollutants (POPs) in the National Health and Nutrition Examination Survey 1999–2006, and examined whether potentially diabetogenic POPs account for associations between lactation and diabetes.

Research design and methods: Among 4479 parous women, breastfeeding history was defined as the number of children breastfed ≥ 1 month. Diabetes was identified by self-report or hemoglobin A1c $> 6.5\%$. Twenty-four POPs were measured in serum among subsamples of 668 to 1073 participants.

Results: Compared with women without lactation history, odds ratios (95% confidence intervals) of having diabetes among those with 1–2 and ≥ 3 lactation periods were 0.83(0.61, 1.13) and 0.63(0.44, 0.91; $P_{trend} = 0.03$). Lifetime lactation history was inversely associated with serum concentrations of 17 out of the 24 organochlorine pesticides, polychlorinated biphenyl congeners (PCBs), and perfluoroalkyl substances ($P_{trend} < 0.05$). Comparing the ≥ 3 lactations group with women without a lactation history, the relative reduction of POPs ranged from 12% (PCB-196) to 30% (oxychlordane). The inverse association between lactation and diabetes was slightly attenuated after adjustment for POPs. Age-stratified analyses showed that the inverse association between lactation periods and serum POP concentrations was observed primarily among participants < 60 years, whereas age did not significantly modify the association between lactation history and diabetes prevalence.

Conclusion: Crudely-classified lifetime lactation history was inversely associated with concurrent serum POP concentrations and diabetes prevalence. Prospective studies are needed to clarify how lactation could complement diabetes prevention through decreasing the POP body burdens.

1. Introduction

Lactation has been linked with a lower risk of chronic diseases (Victora et al., 2016), such as type 2 diabetes, although potential mechanisms remain to be explored (Aune et al., 2014; Gunderson et al., 2015; Jager et al., 2014). Breast milk is known to contain environmental chemicals (Massart et al., 2005; Needham et al., 2011), and lactation is an important excretion route for many of them (LaKind et al., 2001; Massart et al., 2005; Needham et al., 2011), especially those with long elimination half-lives in humans (LaKind et al., 2001; Needham and Wang, 2002). As many environmental chemicals are suspected of being diabetogenic (Kuo et al., 2013; Thayer et al., 2012), the possibility exists that an apparent beneficial effect of lactation could be due to the elimination of diabetogenic chemicals.

Abbreviations: POP, persistent organic pollutants; OCP, organochlorine pesticides; PCDD, polychlorinated dibenzo-p-dioxins; PCDF, polychlorinated dibenzofurans; PFAS, perfluoroalkyl substances; PCB, polychlorinated biphenyl; NHANES, National Health and Nutrition Examination Survey; *p,p′*-DDE, *p,p′*-dichlorodiphenyldichloroethylene; β-HCH, β-hexachlorocyclohexane; 1,2,3,6,7,8-HxCDD, 1,2,3,6,7,8-hexachlorodibenzo-p-dioxin; 1,2,3,4,6,7,8-HpCDD, 1,2,3,4,6,7,8- heptachlorodibenzodioxin; 1,2,3,4,6,7,8,9-OCDD, 1,2,3,4,6,7,8,9-octachlorodibenzodioxin; 1,2,3,4,6,7,8-HpCDF, 1,2,3,4,6,7,8-heptachlorodibenzofuran; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; PFHS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; HbA1c, hemoglobin A1c

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Persistent organic pollutants (POPs) are resistant to degradation in the environment and highly persistent in the human body. These pollutants include organochlorine pesticides (OCP), polychlorinated dibenzo-p-dioxins (PCDD), polychlorinated dibenzofurans (PCDF), polychlorinated biphenyls (PCB), and perfluoroalkyl substances (PFASs) (Vallack et al., 1998). It has been found that lactation could lower the POP burden in mothers (Hooper et al., 2007; Kostyniak et al., 1999; Mondal et al., 2014; Skaare and Polder, 1990; Thomsen et al., 2010; Wang et al., 2009). Although several studies have linked higher POP storage with diabetes risk (Lee et al., 2006; Lind et al., 2014; Suarez-Lopez et al., 2015; Wu et al., 2013), it remains unclear whether potential long-term benefits of lactation on chronic disease risk in women could be attributed to the reduction in POP burden.

Among parous women participating in the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2006, we examined three hypotheses: (1) a lifetime lactation history is associated with lower serum POP concentrations, (2) a lactation history is associated with a lower diabetes risk, whereas higher POP concentrations are associated with a higher diabetes risk, and (3) a lactation history may lower diabetes risk through reducing serum POP concentrations.

2. Methods

2.1. Study population

The continuous NHANES used a complex, multistage, probability sampling design to randomly select a nation-wide representative sample of non-institutionalized U.S. residents every two years (CDC, 2013). The study protocol was approved by the institutional review board at the Centers for Disease Control and Prevention (Atlanta, GA, USA), and written informed consent was obtained from all participants. A total of 10701 women aged ≥ 20 years were surveyed between 1999 and 2006. Among them, we excluded participants who (1) did not complete medical examination (n=919); (2) did not have a pregnancy resulting in a live birth (n=2652), because nulliparous women in NHANES were much younger and their serum POP concentrations were much lower than the others, suggesting a different exposure history; (3) reported current pregnancy or breastfeeding (n=800); (4) reported diabetes diagnosed before last delivery (n=258), to ensure temporal relationship between lactation and diabetes onset; (5) had prevalent cardiovascular disease or cancer (n=1211); or (6) had a missing body mass index (BMI, n=82), leaving 4779 participants for analysis.

2.2. Assessment of reproductive history

During medical examination, trained technicians performed private interviews of female participants aged 12 and above on reproductive history.(CDC, 2015) Women reported number of pregnancies resulting in live birth, age at last birth, number of parity (1–2, 3–4, and ≥ 5), whether they had breastfed any child (yes or no), and number of children breastfed for at least 1 month. Lactation history was categorized into 0 (no lactation), 1–2, or ≥ 3 based on the number of children breastfed for at least 1 month.

2.3. Assessment of serum concentrations of POPs

Procedures for blood collection and processing have been described elsewhere (CDC, 2015). Serum POPs were measured in one thirds of participants who provided blood samples. OCPs, PCDDs, PCDFs, and PCBs were measured in survey years 1999–2004, using high-resolution gas chromatography/isotope-dilution high-resolution mass spectrometry (CDC, 2015). Concentrations were lipid-standardized through dividing POP concentrations by total serum lipids derived using the Philipps formula based on total cholesterol and triacylglycerol (Zong et al., 2015). PFASs were measured in 1999–2000 and 2003–2006, using automated solid-phase extraction coupled to reverse-phase high-performance liquid chromatography/tandem mass spectrometry (Kato et al., 2011). In this study, data on OCPs, PCDDs, PCDFs, and PCBs were available among 1165 participants, whereas PFAS data were available from 1029 participants. POP values below the limit of detection were replaced with limit of detection divided by the square root of 2, according to NHANES analysis recommendation (Zong et al., 2015). In the current study, we focused on chemicals measured in ≥ 2 survey circles (to maintain reasonable sample size) and with $\geq 70\%$ participants having values above the limit of detection (as a trade-off between the number of POPs included in the main analysis and a reasonable percentage of participants with values above the limit of detections to ensure adequate sample variability in POP values for analysis) (Zong et al., 2015). Twenty four POPs in the following groups were analyzed: (1) OCPs and their metabolites, including oxychlordane, trans-nonachlor, *p,p′*-dichlorodiphenyl dichloroethylene (*p,p′*-DDE), and β-hexachlorocyclohexane (β-HCH); (2) PCDDs and PCDFs, including, 1,2,3,6,7,8-heptachlorodibenzo-p-dioxin (1,2,3,6,7,8-HxCDD), 1,2,3,4,6,7,8-octachlorodibenzodioxin (1,2,3,4,6,7,8-HpCDD), 1,2,3,4,6,7,8,9- heptachlorodibenzofuran (1,2,3,4,6,7,8,9-OCDD), and 1,2,3,4,6,7,8-Heptachlorodibenzofuran (1,2,3,4,6,7,8-HpCDF); (3) PCBs, including the dioxin-like PCB-118, PCB-126, and PCB-169, and the non-dioxin like PCB-074, PCB-138, PCB-153, PCB-170, PCB-180, PCB-187, PCB-194, PCB-196, and PCB-199; and (4) PFASs, such as perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA).

2.4. Assessment of diabetes

Diabetes was defined as self-report of physician-diagnosed diabetes, current use of insulin or oral diabetes medications, or hemoglobin A1c (HbA1c) $\geq 6.5\%$ (Kilpatrick et al., 2009). HbA1c concentrations were measured in whole blood using a high-performance liquid chromatography system by the Diabetes Diagnostic Laboratory at the University of Missouri-Columbia in NHANES 1999–2004 and by the Fairview Medical Center Laboratory at the University of Minnesota for 2005–2006 (Carson et al., 2010). HbA1c values were recalibrated for NHANES 2005–2006 to account for the differences in the assays used between laboratories (Carson et al., 2010). Age at diabetes diagnosis was self-reported for participants with known diabetes, or current age for those diagnosed by abnormal HbA1c levels.

2.5. Assessment of covariates

Information on demography, lifestyle, and prevalent diseases was collected using survey questionnaires during in-person interviews (CDC, 2015). Ethnicity was categorized into non-Hispanic white, non-Hispanic black, Mexican, and other ethnic groups including multi-ethnicity. Country of birth was classified as U.S. born and others. Educational attainment was grouped as high school or below, any college, and graduate school or beyond. Smoking status was classified as never smokers, past smoker, and current smokers. Alcohol consumption was divided into abstainers, 1–3 drinks/day, and ≥ 4 drinks/day. Regular moderate-to-vigorous physical activity and family history of chronic diseases (cardiovascular diseases or cancer) was defined as yes or no (Zong et al., 2015). We further adjusted for survey years (1999–2000, 2001–2002, 2003–2004, and 2005–2006) to account for time trends in POP exposures in general populations.