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Exposure to DDT and hypertensive disorders of pregnancy among South African women from an indoor residual spraying region: The VHEMBE study

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ABSTRACT

Indoor Residual Spraying (IRS), the use of insecticides inside residences for malaria control, may cause elevated exposure to insecticides such as dichlorodiphenyl trichloroethane (DDT). Evidence suggests that DDT exposure may increase blood pressure but no study has investigated associations with hypertensive disorders of pregnancy (HDP) in an IRS area. We measured the serum concentration of DDT and its breakdown product dichlorodiphenyl trichloroethylene (DDE) at the time of delivery among 733 rural South African women participating in the Venda Health Examination of Mothers, Babies and their Environment (VHEMBE). We also collected data on HDP diagnosis through questionnaires administered to participants and medical record abstraction. We used multiple logistic regression models to examine the relation between DDT/E and HDP. *p,p′*-DDT and *p,p′*-DDE serum concentrations were associated with HDP based on self-report (OR = 1.50; 95%CI = 1.10, 2.03 for *p,p′*-DDT and OR = 1.58; 95%CI = 1.09, 2.28 for *p,p′*-DDE) and medical records (OR = 1.32; 95%CI = 0.99, 1.75 for *p,p′*-DDT and OR = 1.47; 95%CI = 1.03, 2.09 for *p,p′*-DDE). *p,p′*-DDE was also associated with gestational hypertension (OR = 1.44; 95% CI = 1.00, 2.07). Exposure to DDT and DDE may be associated with elevated risks of HDP in South African women residing in an area sprayed for malaria control.

1. Introduction

Banned in Western countries since the 1970s, dichlorodiphenyl trichloroethane (DDT), an organochlorine insecticide, is sprayed on the interior walls of homes to control malaria in 10 countries – 9 of which are in Africa – as part of Indoor Residual Spraying (IRS) programs (World Health Organization, 2015). IRS results in elevated human exposure to DDT and dichlorodiphenyl dichloroethylene (DDE), DDT's primary breakdown product. For instance, we reported median (interquartile range) *p,p′*-DDT serum concentrations of 736.9 (161.8–1726.7) ng/g-lipid among South African women whose homes were sprayed during pregnancy compared to 50.0 (18.6–236.9) ng/g-lipid for women living in unsprayed homes (Gaspar et al., 2017). These levels are substantially higher than reported in contemporaneous populations of pregnant women or women of reproductive age in the United States (Bradman et al., 2007; Centers for Disease Control and Prevention, 2005). DDT and DDE are highly persistent in biological tissues and the environment, are lipid soluble and can cross the human placenta (Agency for Toxic Substances and Disease Registry, 2002; Falcon et al., 2004).

Although findings have been inconsistent, some studies suggest that exposure to *p,p′*-DDT and *p,p′*-DDE (DDT/E) may be associated with hypertension in humans. In Greenland, plasma *p,p′*-DDT was associated with elevated odds of hypertension among Inuit aged 18–39 years but not in those aged 40 years and older (Valera et al., 2013b) and prenatal exposure to *p,p′*-DDT was associated with elevated risks of hypertension among California women (La Merrill et al., 2013)*p,p′*. In contrast, in another study of Inuit in Nunavik, Canada, *p,p′*-DDT plasma concentrations were associated with lower odds of hypertension while *p,p′*-DDE levels were associated with higher odds (Valera et al., 2013a). *p,p′*-

Abbreviations: BP, blood pressure; CI, confidence interval; GM, geometric mean; GSD, geometric standard deviation; HDP, hypertensive disorders of pregnancy; DDT, Dichlorodiphenyl trichloroethane; DDE, Dichlorodiphenyl dichloroethylene; DDT/E, DDT and DDE; IRS, Indoor Residual Spraying; LOD, limit of detection; LOQ, limit of quantification; OR, odds ratio; PCA, principal component analysis; SD, standard deviation; SES, socioeconomic status; VHEMBE, Venda Health Examination of Mothers, Babies and their Environment

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DDE was also associated with increased odds of hypertension among elderly individuals in Sweden (Lind et al., 2014) but other studies based in the Canary Islands (Henriquez-Hernandez et al., 2014), Alabama, United States (U.S.) (Goncharov et al., 2011) and Granada, Spain (Arrebola et al., 2015) found no association between *p,p′*-DDT or *p,p′*-DDE and blood pressure.

Despite the possible link between exposure to DDT/E and essential hypertension, only one human study has investigated associations with hypertensive disorders of pregnancy (HDP). In that study, Savitz et al. (2014) found no evidence of an association between serum concentrations of *p,p′*-DDT/E and gestational hypertension or preeclampsia among women participating in the Collaborative Perinatal Project conducted between 1959 and 1965 when DDT was still used in the U.S. No previous study has investigated associations between exposure to DDT/E and HDP in areas where DDT is used for IRS and populations may be more susceptible to the toxic effect of DDT than Western populations due to malnutrition, poverty and poor health.

Potential impacts of environmental exposures on HDP is of particular public health significance in sub-Saharan Africa where HDP is the second leading cause of maternal death (Say et al., 2014). In Africa, preeclampsia complicates 2–17% of pregnancies (Osungbade and Ige, 2011; Say et al., 2014) and, at 26%, has a case fatality rate that is orders of magnitude higher than in high-income countries (MacKay et al., 2001). The aim of the present study was thus to evaluate whether maternal serum concentrations of DDT and DDE are associated with elevated risks of HDP among women living in Limpopo Province, South Africa, an area where DDT has been used for IRS for several decades.

2. Methods

2.1. Participants

Data for these analyses were derived from the Venda Health Examination of Mothers, Babies and their Environment (VHEMBE). Methods are described in detail in Gaspar et al. (2017). VHEMBE is a birth cohort study whose objective is to evaluate the relationship between environmental exposures and maternal and child health. Women participating in the VHEMBE study were recruited from Tshilidzini Hospital in the rural Vhembe District of Limpopo Province, South Africa from August 2012 to December 2013 when they presented for delivery. Gravidas were eligible for participation if they were aged 18 years or older, spoke Tshivenda (the most commonly spoken language in the study area) at home, lived within 20 km of the hospital and planned to remain in the area over the following two years, had not been diagnosed with malaria during pregnancy, had contractions > 5 min apart, and gave birth to a viable singleton. Of 920 eligible women, 152 refused enrolment, 3 did not provide a sufficient blood sample for DDT analysis, and 14 did not complete a baseline questionnaire, leaving a sample of 751. For this analysis, we excluded women who reported a diagnosis of nongestational hypertension (n = 18), leaving a final sample of 733 women. Study participants provided informed consent before data collection began. Committees for the Protection of Human Subjects from the University of California, Berkeley, McGill University, University of Pretoria, Limpopo Department of Health and Social Development and Tshilidzini Hospital approved all research activities.

2.2. Data collection

Data were obtained from participants using an interviewer-administered questionnaire conducted shortly after delivery. All interviews were conducted in Tshivenda by trained study staff originating from the local area and fluent in Tshivenda and English. Questionnaires were used to obtain information on HDP diagnosis, sociodemographic indicators, household assets (selected based on the Demographics and Health Survey (United States Agency International Development)), pregnancy and health histories, IRS insecticide application and personal habits. Based on guidelines from Statistics South Africa, we considered the food poverty line to be at 386 South African Rands/month/person (approximately 30 USD) (Statistics South Africa, 2014). The questionnaire was designed in English, translated in Tshivenda and back-translated in English by native speakers in the translated language.

Registered nurses blinded to participant's exposure abstracted hospital medical records to obtain information on diagnosis of gestational hypertension, preeclampsia, gestational age at birth, infant birth weight, and maternal HIV status.

2.3. Measurement of DDT and DDE in maternal serum

Serum samples were collected from women by venipuncture at the time of delivery and were immediately processed and stored at −80 °C until shipment to the Emory University Environmental Health Laboratory where *p,p′*-DDT, *p,p′*-DDE and *o,p′*-DDT were measured using high-resolution gas chromatography-isotope dilution mass spectrometry (Barr et al., 2003). The limits of detection (LOD) for *p,p′*-DDT, *p,p′*-DDE and *o,p′*-DDT were 0.01, 0.03 and 0.01 ng/mL serum, and the limits of quantification (LOQ) were 0.03, 0.09, and 0.03 ng/mL serum, respectively. DDT/E concentrations are expressed on a lipid basis. Total lipids were determined based on triglyceride and total cholesterol serum concentrations measured using standard enzymatic methods (Roche Chemicals, Indianapolis, IN, USA) (Phillips et al., 1989).

2.4. Outcome definitions

Primary outcomes for this study included: 1) Self-reported diagnosis of hypertension, preeclampsia or eclampsia [referred to as self-reported HDP hereafter] during the index pregnancy based on the following question: “Did a doctor or nurse ever tell you that you had high blood pressure or BP, hypertension, eclampsia, or preeclampsia?” and, if the answer was “Yes”, “Was it during this pregnancy?”; and 2) Doctor diagnosis of gestational hypertension, preeclampsia or HDP (gestational hypertension or preeclampsia) based on medical records.

2.5. Statistical analysis

Analysis of variance (ANOVA) was used to examine bivariate associations between categorical variables and DDT/E while Pearson's correlations were used for continuous variables. Multiple logistic regression models were used to evaluate associations between DDT/E and gestational hypertension, preeclampsia or HDP.

Serum concentrations of DDT/E were $\log_{10}$-transformed to reduce the influence of outliers or were categorized into quartiles. We used values generated by the instrument for serum concentrations between the LOD and the LOQ. Values below the LOD were imputed at random based on a log-normal probability distribution whose parameters were determined by maximum likelihood estimation (Lubin et al., 2004). Confounders considered for inclusion in models were identified based on Directed Acyclic Graphs (DAGs) and included the following variables (expressed as shown in Table 1 or in parentheses): maternal age at delivery (continuously); parity; socioeconomic status (SES) indicators (including maternal education, household income per person (continuous), poverty, number of times the mother skipped meals because there was not enough food); diabetes; smoking; alcohol consumption; and season of BP measurement (winter, spring, summer or fall). In addition, we used principal component analysis (PCA) to develop a summary measure of household assets based on guidelines for measuring household wealth in low-income countries (Vyas and Kumaranayake, 2006). Variables included whether a household member owned the following assets: home, watch, car, cellphone with internet, cellphone without internet, landline phone, computer, agricultural land, chickens or livestock, a western-style home compared to a traditional home, bicycle, motorcycle, wheelbarrow, radio, television or a bed to sleep on. We included the first component as a covariate in