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Residential agricultural pesticide exposures and risks of preeclampsia

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ABSTRACT

We investigated risks of preeclampsia phenotypes from potential residential pesticide exposures, including 543 individual chemicals and 69 physicochemical groupings that were applied in the San Joaquin Valley of California during the study period, 1998–2011. The study population was derived from birth certificate data linked with Office of Statewide Health Planning and Development maternal and infant hospital discharge data. The following numbers of women with preeclampsia phenotypes were identified: 1045 with superimposed (pre-existing hypertension with preeclampsia) preeclampsia (265 with gestational weeks 20–31 and 780 with gestational weeks 32–36); 3471 with severe preeclampsia (824 with gestational weeks 20–31 and 2647 with gestational weeks 32–36); and 2780 with mild preeclampsia (207 with gestational weeks 20–31 and 2573 with gestational weeks 32–36). The reference population for these groups was 197,461 women who did not have diabetes (gestational or pre-existing), did not have any hypertensive disorder, and who delivered at 37 weeks or later. The frequency of *any* exposure was lower or about the same in each preeclampsia case group (further delineated by gestational age), and month time period, relative to the frequency in reference population controls. Nearly all odds ratios were below 1.0 for these *any* vs no exposure comparisons. This study showed a general lack of increased risks between a range of agriculture pesticide exposures near women's residences and various preeclampsia phenotypes.

1. Introduction

Preeclampsia, commonly defined as high blood pressure and proteinuria after 20 weeks of pregnancy, affects upwards of 5% of pregnancies and contributes substantially to maternal morbidity and mortality in the United States (Mol et al., 2016). Factors contributing to elevated risks of preeclampsia include nulliparity, African-American race, obesity, nonsmoking, a clinical history of preeclampsia, hypertension, diabetes, and autoimmune conditions (Jeyabalan, 2013). Gene variants in selected pathways such as oxidative stress, inflammation, and angiogenesis have also been put forward as contributors to the risk profile of women who develop preeclampsia (Jebbink et al., 2012).

Environmental exposures have been rarely investigated for their potential etiologic contribution to preeclampsia. Certain pesticide exposures (e.g., organochlorines, have been suggested to elevate risk of hypertensive disorders in general (Morgan et al., 1980; Siddiqui et al., 2002; Rosenbaum et al., 2017; Ledda et al., 2015) and in pregnancy specifically, preeclampsia (Saldana et al., 2009; Nugteren et al., 2012). Despite a few studies suggesting associations, though not all (Willis et al., 1993; Nordby et al., 2006; Saunders et al., 2014), between pesticide exposures and preeclampsia, the scant literature is insufficient to draw clear inferences. In general, such studies have been nonspecific to the pesticide chemical (e.g., any pesticide exposure yes vs no), small in sample size, varied in how women's activities may have facilitated pesticide exposure (e.g., employment or self-reported activities), or did not consider pertinent co-morbidities like gestational diabetes.

To substantially extend the limited extant information, we investigated population-based data on > 200,000 births and proximal residential exposures to more than 500 commercial agricultural

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pesticide active ingredients and adjuvants during multiple gestational time points. The study population derived from the San Joaquin Valley of California, one of the highest agricultural pesticide use areas in the US.

2. Materials and methods

2.1. Study population

This study was approved by the Stanford University Institutional Review Board and the California State Committee for the Protection of Human Subjects.

Data for this case-control study derive from 1998 to 2011 California births to women residing in the San Joaquin Valley (Fresno, Kern, Kings, Madera, Merced, San Joaquin, Stanislaus, and Tulare counties). In this region and time period there were 892,088 livebirths delivered in non-military hospitals. We restricted the study to those with gestational ages 20–41 weeks (determined by obstetric estimate for 2007–11 and by last menstrual period for 1998–2006), birth weights between 500 and 5000 g, and singleton births – a total of 771,416 births. This analysis was an opportunistic extension of a previously conducted study specific to preterm birth (Shaw et al., 2018) whereby the 771,416 eligible births were 78,421 preterm (i.e., < 37 weeks gestation) and 692,995 term (i.e., > 37 weeks gestation). For analytic efficiency that study was based on a randomly selected group of 235,263 (from the 692,995) term births in a 3:1 ratio of term to preterm infants.

For each of these 313,684 (78,421 + 235,263) births, we obtained the mother's residential address at the time of delivery from the electronic birth certificate. A REST API Geocode Service maintained by the California Department of Public Health Information Technology Services Division was used to geocode addresses. This service standardizes, verifies, and corrects addresses before matching against multiple address-attributed reference databases. Successful geocoding was achieved for 295,387 births (94%).

We further linked the 295,387 births with Office of Statewide Health and Planning (OSHPD) maternal and infant hospital discharge data. This linkage allowed for information on a range of maternal and pregnancy characteristics found on the birth certificate paired with clinical detail from the delivery hospitalization for practically all inpatient live births. The algorithm employed for this linkage is accurate and previously described (Herrchen et al., 1997; Lyndon et al., 2012). Successful linkage was achieved for 99% (n = 293,044).

Our analytic goal was to investigate various preeclampsia phenotypes among pregnancies that delivered before 37 weeks gestation. To identify preeclampsia as well as other comorbidities from hospital discharge data, we employed International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes. Included as comorbidities were pre-existing diabetes (Type 1 (250.x1, 250.x3) and Type 2 (250.x0, 250.x2, 648.0)) and gestational diabetes (648.8). For hypertensive disorders we identified: pre-existing hypertension (401–405, 642.0, 642.1, 642.2, 642.9); gestational hypertension (642.3); mild preeclampsia (642.4); severe preeclampsia/eclampsia (642.5, 642.6); and preeclampsia or eclampsia superimposed on pre-existing hypertension (642.7). Women with multiple ICD9 codes for hypertensive disorders were reclassified to allow for mutually exclusive groups. Specifically, women with multiple codes were classified as: women with a pre-existing hypertension code and a preeclampsia or eclampsia code were classified as having preeclampsia or eclampsia superimposed on pre-existing hypertension; women with pre-existing hypertension and gestational hypertension were classified as having pre-existing hypertension; and women with multiple codes for gestational hypertension and preeclampsia or eclampsia were classified as the most severe condition. Thus, for our primary analytic queries women were grouped into one of 3 “case” phenotypic groups: 1) preeclampsia or eclampsia superimposed on pre-existing hypertension; 2) severe preeclampsia/eclampsia; and 3) mild preeclampsia. The 3 preeclampsia phenotypic groups were further stratified by gestational age of delivery as 20–31 weeks or 32–36 weeks. Women who delivered in the study period who did not have diabetes (gestational or pre-existing), did not have any hypertensive disorder (including preeclampsia), and who delivered at 37 weeks or greater served as the referent population (controls).

2.2. Pesticide and adjuvant compounds studied

We assessed exposure to 543 individual chemicals used as pesticides or as adjuvants in pesticide products or application mixtures and 69 physicochemical groupings having the same chemical classification and proven or putative mechanism of action (e.g., organophosphates) that were applied at > 100 lb in any of the 8 San Joaquin Valley counties in any year during the study period, 1998–2011 (California-Department-of-Pesticide-Regulation, 2013; Pesticide Use Reporting). Low-toxicity chemicals such as biopesticides (e.g., microbial pesticides, soaps, essential oils), low-toxicity inorganic compounds (e.g., sulfur, kaolin clay), and other compounds determined by US EPA to have low toxicity, as described in US EPA Risk Assessment documents for each chemical were excluded (EPA-U.S.-Environmental-Protection-Agency, 2013, Pesticide Chemical Search). In addition, compounds were flagged as having reproductive or developmental toxicity based on the California Proposition 65 list (California-Office-of-Environmental-Health-Hazard-Assessment, 2012) or as endocrine disruptors (Colborn T; European-Commission, 2012; Keith, 1997). Chemicals with a US EPA-determined Reference Dose based on a toxicological study with a reproductive or developmental endpoint as described in EPA risk assessment documents were included (EPA-U.S.-Environmental-Protection-Agency, 2013. Pesticide Chemical Search).

2.3. Pesticide exposure assessment

To estimate pesticide exposures, we assigned a time window of exposure for each case or control woman from one month before conception (B1) to date of delivery by every 4 weeks of pregnancy (P1-P9).

To estimate pesticide applications, we obtained statewide Pesticide Use Reporting (PUR) records from the California Department of Pesticide Regulation describing agricultural pesticide applications occurring between 1 January 1998 and 31 December 2011 (California-Department-of-Pesticide-Regulation, 2013. Pesticide Use Reporting). These data are submitted by county agriculture commissioners and are spatially referenced to public land survey sections (PLSS). For the study period, the total number of active ingredient daily production agricultural use records with a PLSS specified, and for the 543 chemicals that were present in PUR records, exceeded 24 million. Following the method of Rull and Ritz (2003), we spatially refined PLSS polygons through overlay of matched land-use survey field polygons provided by the California Department of Water Resources. We matched each PUR record to the land-use survey conducted closest in time to the application date (surveys are conducted roughly every 5–7 years in each California county). Matching is based on PLSS and crop type as specified in records. Infrequently rotated crops, such as orchard crops and vineyards, were matched one-to-one, while frequently rotated crops, such as field and truck crops, were grouped together in a single category, and non-agricultural land-uses were subtracted from PLSS polygons when no crop types were matched to available polygons. Of the total applications (and active-ingredient poundage) recorded spanning 1998–2011 for the 543 chemicals of interest, > 90% were successfully linked to polygons. For those where no field polygon was specified, no spatial refinement was possible. We determined temporal proximity by comparing recorded dates of applications, believed to be accurate within a few days, to the time window of exposure for each case or control woman.

To assign exposure, we utilized the CEHTP Pesticide Linkage Tool, a custom-developed Java (Oracle, Redwood Shores, CA) application that