Chemosphere 262 (2021) 128309

Contents lists available at ScienceDirect

Chemosphere

journal homepage: www.elsevier.com/locate/chemosphere

Associations of PCBS, dioxins and furans with follicle-stimulating hormone and luteinizing hormone in postmenopausal women: National Health and Nutrition Examination Survey 1999–2002

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HIGHLIGHTS

- Lower luteinizing hormone with exposure to anti-estrogenic and dioxin-like POPs.
- No overall association of follicle-stimulating hormone with PCBs, dioxins or furans.
- Stronger impact postmenopausal women with elevated C-reactive protein or adiposity.
- Adiposity primarily impacted associations with dioxin-like and anti-estrogenic POPs.

ARTICLE INFO

Article history:
Received 1 August 2020
Received in revised form
1 September 2020
Accepted 9 September 2020
Available online 11 September 2020

Handling Editor: Shane Snyder

Keywords:
Follicle stimulating hormone
Luteinizing hormone
PCBs
Dioxins
Endocrine disruption

ABSTRACT

Background: The general population is exposed to the group of endocrine disrupting chemicals persistent organic pollutants (POPs), that includes polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs).
Objectives: The aim of this research was to evaluate the associations of serum levels of PCB, PCDD, and PCDF congeners with follicle stimulating hormone (FSH) and luteinizing hormone (LH) in postmenopausal women not taking exogenous hormones. We hypothesized that associations of POPs with these gonadotropins could be modified by factors affecting endogenous hormones.
Methods: Cross-sectional analyses were conducted on data from 89 postmenopausal women using data from the National Health and Nutrition Examination Survey (NHANES). POPs were summarized based on classification schemes thought to reflect toxicological properties. Associations of POPs and gonadotropin hormones were modeled with multivariable regression models. When evidence of interaction was found, conditional effects were estimated.
Results: We found inverse associations of LH, but not FSH, with exposure to anti-estrogenic and/or dioxin-like POPs, but not with non dioxin-like PCBs. A doubling of dioxin-like toxic equivalents (TEQs) was associated with a decrease in LH of 11.9% (95% CI = −21.3%, −1.4%, p = 0.03). Inverse associations were enhanced by potential effect modifiers related to both direct and indirect estrogenicity, including obesity and the obesity-related condition inflammation.
Conclusions: These investigations support a pattern of endocrine-disrupting effects by dioxin-like POPs among postmenopausal women, especially those with conditions related to peripheral estrogenicity.

1. Introduction

Polychlorinated biphenyls (PCBs) are a class of heat-resistant, oily liquids that were used as insulating fluids in capacitors and transformers (ATSDR, 2000). Polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs), commonly

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https://doi.org/10.1016/j.chemosphere.2020.128309
0045-6535/

known as dioxins, are compounds formed from a variety of sources, including as unintentional by-products of industrial processes (Fiedler, 1996). Like PCBs, dioxins are resistant to abiotic and biotic degradation in the environment and bioaccumulate and magnify in animals and humans (Safe, 1994; Van den Berg et al., 1998). Human body burdens of these chemicals have declined over time (Aylward and Hays, 2002; Turyk et al., 2012), with continued exposure through inhalation as well as consumption of contaminated food items (van Larebeke et al., 2001).

Persistent organic pollutants (POPs), including PCBs, PCDFs and dioxins, exhibit a broad range of toxic effects including disruption of sex steroid hormone homeostasis. Dioxin-like compounds, acting through the AhR, are thought generally to be antiestrogenic, although data showing positive associations with estrogen dependent tumors (van Larebeke et al., 2001; Ohtake et al., 2003) and the upregulation of genes related to the enzyme CYP 19, which encodes aromatase activity (Warner et al., 2012), also suggest estrogen-like activity. Effects of PCBs on sex steroid hormones are varied, with some congeners thought to be estrogenic and some, more dioxin-like, antiestrogenic. Additional mechanisms suggested for effects of PCBs and their metabolites on steroid hormones relate to inhibition of estrogen sulfotransferases (Kester et al, 2000, 2002) and decreased sex hormone binding globulin (SHBG), leading to greater bioavailability of peripheral sex hormones as well as direct action on hypothalamic gonadotropin releasing hormone gene expression (Gore et al., 2002).

Studies in male and female animals and in vitro investigations have also shown direct effects of dioxins on the pituitary hormones follicle stimulating hormone (FSH) and luteinizing hormone (LH) as well as associations between PCB exposure and FSH and LH levels, although results have been inconsistent and differed by PCB congener or Aroclor (Desaulniers et al., 1999; Wade et al., 2002; Oskam et al., 2005; Uslu et al., 2013; Taketoh et al., 2007; Cao et al., 2011).

To date, there is only one known study in occupationally exposed postmenopausal women that found an inverse association between PCBs and FSH (Persky et al., 2011). In one of two other investigations of premenopausal women during days 1–5 of the menstrual cycle, PCBs were inversely associated with FSH (Pan et al., 2019). In the other study there were no associations with individual gonadotropins, but a positive association with the FSH:LH ratio (Gallo et al., 2018). Relationships of PCBs with gonadotropins in men have been inconsistent (Emeville et al., 2013; Ferguson et al., 2012; Richthoff et al., 2003; Hagmar et al., 2001; Persky et al 2001, 2012; Haugen, 2011; Vested, 2014; Giwercman et al., 2006; Sweeney et al., 1997; Petersen et al., 2018; Vitku et al., 2016).

In this investigation, we explored associations of POP exposure with FSH and LH levels in postmenopausal women using the National Health and Nutrition Examination Survey (NHANES), a cross-sectional survey examining a representative sample of the US population. The present study uses PCB, PCDD, PCDF, FSH, and LH measurements obtained in the 1999–2000 and 2001–2002 survey cycles. We examined the effects of POP exposures, grouped into categories with similar structure or a common mechanism of action, on FSH and LH in a subgroup of postmenopausal women not taking glucocorticoids or sex hormones. In addition, we examined the hypothesis that associations of POPs with FSH and LH are modified by factors that may influence endogenous hormones.

2. Methods

2.1. Participants

Data from the NHANES survey cycles conducted in 1999–2000 and 2001–2002 were obtained online. Each survey is a nationally representative sample of the US civilian, noninstitutionalized population based on a complex probability sampling design. The University of Illinois at Chicago Institutional Review Board has determined that analysis of NHANES data does not meet the definition of human subject research as defined by 45 CFR 46.102(f).

Any associations between POPs and gonadotropins may be more clearly observed among postmenopausal women who do not require precise timing with the menstrual cycle. Menopause is defined as one year after the permanent cessation of menstrual periods, which women experience at the average age of 51 years. Menopause can occur naturally or be induced through a medical intervention such as bilateral oophorectomy. Normal FSH levels for premenopausal women are 4.7–21.5 mIU/mL, while normal FSH levels for postmenopausal women are 25.8–134.8 mIU/mL (Lobo, 2007). Standards used to define menopause were based on a prior report (Kalkwarf et al., 2003) and were applied consecutively so that the rules were applied only to women not already in a previous category. The following are inclusion categories for postmenopausal women:

1. Any age and last period ≥12 months without hysterectomy or with hysterectomy and bilateral oophorectomy
2. 56–59 years of age and last period ≥12 months with hysterectomy and without bilateral oophorectomy, and FSH ≥25.8 mIU/mL
3. <56 years of age and last period ≥12 months with hysterectomy, without bilateral oophorectomy, and FSH ≥50 mIU/mL

In the present investigation, we focused on the 1847 postmenopausal women ≥40 years of age with questionnaire data that included hysterectomy, bilateral oophorectomy, and prescription medications. Serum levels of gonadotropins were originally used by NHANES investigators to classify women according to menopausal status; therefore, FSH and LH tests were performed only on women aged 35–60 years. We excluded postmenopausal participants who were <40 years of age (n = 3), were <60 years of age with FSH <25.8 mIU/mL (n = 10), if they did not have data on exposure and hormone measures (n = 1697), those with missing cotinine data (n = 1), those who reported taking glucocorticoids (n = 3), and those who specified taking sex hormones (estrogen, progestins, sex hormone combinations, miscellaneous sex hormones, gonadotropin-releasing hormones and analogs, androgens and anabolic steroids, and contraceptives) or other hormones/hormone modifiers, including selective estrogen receptor modulators, aromatase inhibitors, antiandrogens, and antigonadotropic agents (n = 44). Data for analysis of the associations of POPs with FSH and LH were available for 89 participants.

2.2. Follicle-stimulating hormone, luteinizing hormone, and other physiological measurements

Details of the NHANES laboratory measurements are available online for 1999–2000 (CDC, 2020a) and 2001–2002 (CDC, 2020b). Briefly, serum FSH and LH concentrations for 1999–2000 were measured by a microparticle enzyme immunoassay technology. The sensitivity for FSH was 0.2 IU/L and the sensitivity for LH was 0.5 IU/L. Serum FSH and LH concentrations for 2001–2002 were measured by a paramagnetic particle, chemiluminescent two-step enzyme assay. The sensitivity for FSH and LH was 0.02 IU/L. Measurements below the limit of detection (LOD) were assigned a value of 0.2 or 0.5 IU/L divided by the square root of two by the CDC. The inter-assay coefficient of variation (CV) for 1999–2000 varied from 2.37 to 7.95 for FSH and from 1.65 to 7.59 for LH, and the CV for 2001–2002 varied from 3.2 to 7.2 for FSH and from 3.3 to 10.1 for

LH. C-reactive protein (CRP) levels were measured by latex-enhanced nephelometry with high sensitivity by using a Dade Behring Nephelometer II Analyzer System (Dade Behring Diagnostics, Inc., Somerville, New Jersey). Serum total cholesterol was measured enzymatically after hydrolyzation and oxidation, while triglycerides were analyzed enzymatically after hydrolyzation into glycerol.

2.3. Polychlorinated biphenyl, polychlorinated dibenzo-p-dioxin, and polychlorinated dibenzofuran measurements

All POPs were measured in serum by high-resolution gas chromatography/isotope-dilution high-resolution mass spectrometry (Organic Toxicology Branch, National Center for Environmental Health, CDC, Atlanta, Georgia). The congener groupings used in the current study are listed in Table 1. Compounds able to bind to the AhR (PCDDs, PCDFs, and dioxin-like PCBs) were used to calculate TEQs by multiplying the TEQ factor by the congener concentration (Van den Berg et al., 2006) and then summing the values to yield ∑TEQs. PCB congeners were summed to yield ∑PCBs. The PCB congeners were grouped according to structure, including ∑non-dioxin-like PCBs, ∑mono-*ortho* PCBs, and ∑dioxin-like PCBs (consisting of non-*ortho* and mono-*ortho* PCBs), and were also grouped according to mechanism of action, including estrogenic and anti-estrogenic activity (Wolff et al., 1997; Cooke et al., 2001). Polychlorinated biphenyl 126 is listed in both ∑Cooke estrogenic PCBs and ∑Cooke anti-estrogenic PCBs. For congeners with results below the LOD, the measurement was imputed by CDC as the LOD for that specific congener divided by the square root of two. In the first study cycle, more of the individual congener measurements were below the LOD than in the second study cycle. Only congeners that had >10% of results > LOD for each of the two study cycles were included in the analysis. When results for more than one congener were not reported by CDC for a participant, the participant was coded as missing for each summary exposure mentioned previously. However, ∑Wolff estrogenic PCBs comprised two congeners; therefore, the participant was coded as missing if one of the congeners was not reported by CDC.

2.4. Covariates

Potential confounders and effect modifiers evaluated in this study included age, alcohol consumption, BMI, CRP, cotinine level, lipids, race/ethnicity, study cycle, antidiabetic medications, and thyroid hormone medications. Alcohol consumption was dichotomized as <12 drinks/year and ≥12 drinks/year ("Had at least 12 alcohol drinks/1 year?"). Serum cotinine was dichotomized as ≤10 ng/mL and >10 ng/mL, a cutoff previously used as a marker for both active smoking and high environmental tobacco smoke exposure (Pirkle et al., 1996). Participants were classified as Caucasian, African American, or other. We calculated total serum lipids using the formula: lipids = [total cholesterol (mg/dL) x 2.27] + triglycerides (mg/dL) + 62.3 (Phillips et al., 1989). Lipids and CRP were analyzed as continuous measures. Finally, we evaluated medications that can affect hormone homeostasis including antidiabetic and thyroid hormones.

2.5. Statistical analyses

Statistical analyses were performed with SAS 9.2 (SAS Institute Inc., Cary, North Carolina) without the use of sample weights due to the limited sample size. Results were considered significant at $p < 0.05$ and borderline significant at $0.05 < p < 0.10$.

Natural log transformations of exposures, CRP and lipids were used to approximate a normal distribution, with geometric means presented for descriptive purposes. Differences in demographics, health and lifestyle factors, medication use, and study cycle by POPs and hormones were examined using Student's t-tests for continuous variables or Chi-square tests for dichotomous variables. We used analysis of variance with Tukey post hoc testing to evaluate differences in exposure or outcome measures among race categories. Associations between continuous variables were tested with Pearson's correlation coefficients.

Associations of POPs with gonadotropins were estimated using linear regression. For all analyses, we used natural log transformations of continuous measurements of wet weight PCB, PCDD, and PCDF congeners rather than lipid-standardized measurements (Schisterman et al., 2005). FSH and LH were log transformed for regression analysis since model fit, as judged by r-square, was improved compared with non-transformed models. Age, BMI, and lipids were included in all adjusted models. We estimated the percent change in FSH and LH levels for a doubling of serum POPs as $(e^{(\ln 2 \times \beta)} - 1) \times 100$, with 95% confidence intervals (CIs) calculated as $(e^{[\ln 2 \times (\beta \pm 1.96 \times SE)]} - 1) \times 100$.

To assess confounding, additional covariates were added individually to the adjusted model. Confounding was identified by a change in the exposure beta coefficient of more than 10% after the addition of a potential confounder. Effect modification was evaluated using variables indicating the product of the potential effect modifier (CRP, BMI, thyroid medication use, diabetes medication use, serum cotinine) with the exposure. When significant interaction was found ($p < 0.05$), conditional effects at the 25th and 75th

Table 1
Congener groupings for exposure measurements.

Grouping	Congeners[a]
∑TEQs[a]	PCB congeners **105, 118, 126, 156, 169**; PCDD congeners **1,2,3,7,8-PentaPCDD, 1,2,3,6,7,8-HexaPCDD, 1,2,3,7,8,9-HexaPCDD, 1,2,3,4,6,7,8-HeptaPCDD, 1,2,3,4,6,7,8,9-OctaPCDD**; PCDF congeners **2,3,4,7,8-PentaPCDF, 1,2,3,4,7,8-HexaPCDF, 1,2,3,6,7,8-HexaPCDF, 1,2,3,4,6,7,8-HeptaPCDF**
∑PCBs[b]	**74, 99, 105, 118, 126, 138, 146, 153, 156, 169, 170, 177, 178, 180, 183, 187**
∑Non-dioxin-like PCBs[b]	**74, 99, 138, 146, 153, 170, 177, 178, 180, 183, 187**
∑Mono-ortho PCBs[a]	**105**, 114, **118**, 123, **156**, 157, 167, 189
∑Dioxin-like PCBs[a]	77, 81, **105**, 114, **118**, 123, **126**, **156**, 157, **169**, 189
∑Cooke estrogenic PCBs[a]	1, 3, 4, 8, 15, 18, 21, 31, 44, 47, 48, 49, 52, 54, 61, 70, 75,77, 80, 95, **99**, 101, 104, 110, **126**, 136, **153**, 155, 184, 188
∑Wolff estrogenic PCBs[a]	101, 174, **177**, **187**, 201
∑Cooke anti-estrogenic PCBs[a]	37, 77, 81, **105**, 114, **126**[c], 155, **156**, **169**
∑Wolff anti-estrogenic PCBs[a]	66, **74**, 77, **105**, **118**, **126**[c], 155, **156**, **169**

[a] Congeners in bold were included in the grouping.
[b] Only measured congeners in the grouping are shown.
[c] PCB 126 is listed in both ∑Cooke estrogenic PCBs and ∑Cooke anti-estrogenic PCBs.

percentile of the modifier were estimated.

3. Results

3.1. Descriptive statistics

The mean age was 54.3 years (range 42–60 years) and mean BMI was 29.5 kg/m^2 (range 18.4–46.9 kg/m^2) (Table 2). About 36% were Caucasian, 25% African American, and the remainder other or multiple race/ethnicities; 53% reported having 12 or more alcohol drinks/year; 34% had elevated cotinine levels, 11.2% were taking thyroid hormones and 18% using antidiabetic medications (data not shown). For participants with elevated cotinine (>10 ng/mL), 86.7% reported smoking cigarettes every day or some days (data not shown). The mean FSH level (mIU/mL) was 68.6 and ranged from 27.9 to 196.1, and one participant had an FSH level notably above the reference range for postmenopausal women. The mean LH level was 37.6 (mIU/mL) and ranged from 10.2 to 91.0 (Table 2). There were no significant differences between the 1999–2000 and 2001–2002 study cycles for continuous or categorical variables.

3.2. Bivariate analyses

In unadjusted analyses, POP exposures and CRP were significantly higher in African Americans than Caucasians (data not shown). Body mass index and CRP were also significantly higher, while mean FSH was significantly lower, in antidiabetic medication users (data not shown). CRP was significantly lower in participants who specified an alcohol consumption of ≥12 drinks/year. Table 3 shows unadjusted Pearson's correlation coefficients among continuous measures. Luteinizing hormone was significantly and positively related to FSH ($r = 0.77$), and was inversely associated with ∑TEQs ($r = -0.26$); somewhat weaker associations were noted with ∑mono-*ortho* PCBs ($r = -0.22$) and ∑Wolff anti-estrogenic PCBs ($r = -0.20$). In general, POP groupings were significantly and positively associated with lipids.

3.3. Associations of PCBs, dioxins and furans with gonadotropins

In analyses adjusted for age, BMI, and lipids (Table 4), LH was significantly and inversely associated with ∑TEQs, ∑mono-ortho PCBs and ∑Cooke antiestrogenic PCBs. A doubling of ∑TEQs was associated with a decrease in LH of 11.9% (95% CI = −21.3%, −1.4%, $p = 0.03$). The inverse associations of ∑dioxin-like and Wolff anti-estrogenic PCBs with LH were of borderline significance. No significant or borderline significant associations were found between POPs and FSH.

3.4. Effect modification

Effect modification by factors that may influence endogenous hormones, namely BMI, CRP, thyroid medication use, diabetes medication use and serum cotinine levels, was evaluated in adjusted regression models by including a variable indicating the product of the modifier with the exposure. When significant interaction was identified ($p < 0.05$), conditional estimates were generated for associations of POPs with gonadotropins at the 25th and 75th percentiles of the modifier (Table 5). We found evidence for modification of POP/gonadotropin associations by BMI and CRP, even when a main effect was not present. There were stronger inverse associations in women with elevated CRP for LH with non-dioxin-like, mono-*ortho*, dioxin-like, Cooke anti-estrogenic and both Cooke and Wolff estrogenic PCBs; similarly there were stronger associations in women with higher CRP for FSH with TEQs and with total, mono-*ortho*, dioxin-like, Cooke and Wolff anti-estrogenic PCBs. Women with higher BMI had stronger inverse associations of LH with total, dioxin-like and Cooke anti-estrogenic PCBs; women with higher BMI had stronger inverse associations of FSH with TEQs, total PCBs and both Cooke and Wolff antiestrogenic PCBs. There was a lack of support for modification of POP/gonadotropin associations by cotinine, thyroid medication use, and diabetes medication use.

3.5. Sensitivity analyses of associations of POPs with gonadotropins

The majority of participants with the absence of menstrual periods for 12 months or more specified the reason for not having regular periods as "going/gone through menopause." Only three postmenopausal women specified "medical conditions/treatments" as the reason for not having regular menstrual periods (two of the three were 60 years of age). One of these participants reported the use of thiazolidinediones (TZDs), which are a class of insulin-sensitizing agents used to treat diabetes and may affect estrogen metabolism as a result of inhibition of aromatase activity

Table 2
Demographic characteristics and biomarkers in postmenopausal women.

Characteristic	n	Mean[a]	95% CI	Percentile		
				25th	50th	75th
Ln∑TEQs (pg/g)	66	0.11	0.09–0.13	0.07	0.10	0.14
Ln∑PCBs (ng/g)	70	1.2	1.2–1.8	0.9	1.4	2.2
Ln∑Non-dioxin-like PCBs (ng/g)	87	1.3	1.1–1.5	0.8	1.3	1.9
Ln∑Mono-*ortho* PCBs (ng/g)	89	0.19	0.17–0.23	0.12	0.18	0.29
Ln∑Dioxin-like PCBs (ng/g)	70	0.20	0.16–0.24	0.12	0.18	0.30
Ln∑Cooke estrogenic PCBs (ng/g)	89	0.39	0.33–0.46	0.26	0.42	0.63
Ln∑Wolff estrogenic PCBs (ng/g)	87	0.11	0.09–0.12	0.06	0.10	0.16
Ln∑Cooke anti-estrogenic PCBs (ng/g)	70	0.08	0.07–0.10	0.05	0.08	0.11
Ln∑Wolff anti-estrogenic PCBs (ng/g)	70	0.28	0.24–0.34	0.17	0.26	0.39
FSH (mIU/mL)[b]	89	68.6	62.8–74.4	50.0	64.9	85.7
LH (mIU/mL)[c]	89	37.6	34.4–40.9	26.4	35.4	45.6
Age (years)	89	54.3	53.3–55.3	51	55	59
BMI (kg/m^2)	89	29.5	28.3–30.7	25.3	29.4	32.9
LnLipids (mg/dL)	89	675.1	647.3–704.0	606.4	663.4	735.0
LnCRP (mg/dL)	89	0.32	0.26–0.39	0.16	0.34	0.73
Family PIR	89	2.5	2.2–2.8	1.3	2.2	3.5

[a] Mean or geometric mean.
[b] Normal FSH levels for postmenopausal women are 25.8–134.8 mIU/mL.
[c] Normal LH levels for postmenopausal women are 10.0–54.7 mIU/mL.

Table 3
Pearson's correlation coefficients among biomarkers and demographic characteristics in 89 postmenopausal women.

	∑TEQs	∑PCBs	∑NDL	∑MO	∑DL	∑CE	∑WE	∑CA	∑WA	FSH	LH	Age	BMI	Lipids	CRP	PIR
∑TEQs		0.72*	0.70*	0.81*	0.81*	0.68*	0.79*	0.75*	0.79*	−0.12	−0.26*	0.018	0.070	0.46*	0.21	−0.11
∑PCBs	0.72*		0.99*	0.92*	0.92*	0.99*	0.94	0.92*	0.92*	0.00	−0.13	0.00	−0.05	0.24*	0.01	−0.03
∑NDL	0.70*	0.99*		0.89*	0.89*	0.99*	0.93*	0.91*	0.90*	−0.02	−0.11	0.05	−0.07	0.17	−0.07	0.03
∑MO	0.81*	0.92*	0.89*		0.99*	0.87*	0.82*	0.94*	0.99*	−0.14	−0.22*	0.06	0.04	0.29*	0.08	−0.08
∑DL	0.81*	0.92*	0.89*	0.99*		0.89*	0.83*	0.93*	0.99*	−0.08	−0.19	0.03	0.04	0.33*	0.14	−0.12
∑CE	0.68*	0.99*	0.99*	0.87*	0.89*		0.89*	0.89*	0.90*	−0.04	−0.14	0.02	−0.04	0.17	−0.06	0.08
∑WE	0.79*	0.94*	0.93*	0.82*	0.83*	0.89*		0.85*	0.82*	−0.07	−0.13	0.03	−0.05	0.16	−0.04	−0.10
∑CA	0.75*	0.92*	0.91*	0.94*	0.93*	0.89*	0.85*		0.93*	0.00	−0.17	−0.02	−0.08	0.33*	0.04	−0.01
∑WA	0.79*	0.92*	0.90*	0.99*	0.99*	0.90*	0.82*	0.93*		−0.06	−0.20	0.06	0.02	0.31*	0.13	−0.09
FSH	−0.12	0.01	−0.02	−0.14	−0.08	−0.04	−0.07	0.00	−0.06		0.77*	−0.16	−0.38*	−0.02	−0.16	0.23*
LH	−0.26*	−0.13	−0.11	−0.22*	−0.19	−0.14	−0.13	−0.17	−0.20	0.77*		−0.17	−0.26*	−0.09	−0.15	0.07
Age	0.02	0.00	0.05	0.07	0.03	0.02	0.03	−0.02	0.06	−0.16	−0.17		0.01	−0.10	−0.08	0.03
BMI	0.07	−0.05	−0.07	0.04	0.04	−0.04	−0.05	−0.08	0.01	−0.38*	−0.26*	0.01		0.03	0.46*	−0.08
Lipids	0.46*	0.24*	0.17	0.29*	0.33*	0.17	0.16	0.33*	0.31*	−0.02	−0.09	−0.10	0.03		0.19	−0.10
CRP	0.21	0.01	−0.07	0.08	0.14	−0.06	−0.04	0.04	0.13	−0.16	−0.15	−0.08	0.46*	0.19		−0.26*
PIR	−0.11	−0.03	0.03	−0.08	−0.12	0.08	−0.10	−0.01	−0.09	0.23*	0.07	0.03	−0.08	−0.10	−0.26*	

*p < 0.05 Exposures, lipids and CRP were natural-log transformed.
NDL = non-dioxin-like PCBs; MO = mono-*ortho* PCBs; CE=Cooke estrogenic PCBs; WE=Wolff estrogenic PCBs; CA=Cooke anti-estrogenic PCBs; WA=Wolff anti-estrogenic PCBs.

Table 4
Associations of PCBS, dioxins and furans with gonadotropins in postmenopausal women.

		LnFSH			LnLH		
LnPOP	n	Effect estimate[a]	95% CI	p-value	Effect estimate[a]	95% CI	p-value
∑PCBs	70	−2.5	−9.5, 5.1	0.51	−6.5	−14.0, 1.6	0.11
∑NDL PCBs	87	−2.5	−9.5, 5.1	0.51	−5.5	−12.9, 2.5	0.17
∑MO PCBs	89	−6.1	−13.1, 1.5	0.11	**−8.6**	**−16.1, -0.4**	**0.04**
∑DL PCBs	70	−4.2	−11.5, 3.6	0.27	**−7.7**	**−15.5, 0.8**	**0.07**
∑TEQs	66	−7.6	−16.6, 2.5	0.13	**−11.9**	**−21.3, -1.4**	**0.03**
∑CA PCBs	70	−4.5	−12.9, 4.8	0.32	**−10.7**	**−19.4, -1.1**	**0.03**
∑WA PCBs	70	−3.5	−11.0, 4.5	0.37	**−8.2**	**−16.0, 0.3**	**0.06**
∑CE PCBs	89	−2.8	−8.9, 3.7	0.39	−5.5	−12.0, 1.5	0.12
∑WE PCBs	87	−4.1	−11.4, 3.7	0.29	−5.8	−13.6, 2.7	0.17

NDL = non-dioxin-like PCBs; MO = mono-*ortho* PCBs; DL = dioxin-like PCBs; CE=Cooke estrogenic PCBs; WE=Wolff estrogenic PCBs; CA=Cooke anti-estrogenic PCBs; WA=Wolff anti-estrogenic PCBs.
[a] Models adjusted for age, BMI, and lnlipids. Effect estimates are the percent change in the gonadotropin with a doubling in POPs exposure.

(Seto-Young et al., 2011). Exclusion of these three participants in a sensitivity analysis yielded somewhat increased effect estimates. Associations of LH with total, dioxin-like PCBs and Wolff's anti-estrogenic PCBs were significant ($p < 0.05$) as were associations of FSH with ∑TEQs and ∑mono-*ortho* PCBs.

Compared with natural menopause, oophorectomy in postmenopausal women has been shown to lower androgen levels (Laughlin et al., 2000; Labrie et al., 2011); therefore, we repeated the current analysis excluding 10 postmenopausal participants with bilateral oophorectomy. This exclusion decreased effect estimates, and only associations of LH with ∑TEQs and ∑Cooke anti-estrogenic PCBs remained borderline significant, which may be the result of reduced sample size. Repeating the analysis with exclusion of an FSH level notably outside of the laboratory range produced results that were unchanged.

4. Discussion

4.1. Follicle-stimulating hormone and luteinizing hormone

In this investigation, we found inverse associations of anti-estrogenic and/or dioxin-like POP groupings with LH, but not FSH, in postmenopausal women not taking glucocorticoids or sex hormones. Inverse associations of dioxin-like POPs with LH and/or FSH were stronger in participants with elevated CRP or BMI.

In a previous investigation of postmenopausal women with occupational exposures, PCBs were inversely associated with FSH (Persky et al., 2011). In one study of premenopausal women without ovarian insufficiency in whom blood was obtained in the first five days of the menstrual cycle there was also a negative association of PCBs with FSH (Pan et al., 2019). In another study of premenopausal women in which blood was obtained at day 3 of the menstrual cycle there was no association with either FSH or LH, although there was a positive association of estrogenic PCBs with the FSH:LH ratio (Gallo et al., 2018) Studies in men have also not been consistent. In several studies representing a range of exposure levels, PCBs were not associated with FSH or LH. These include healthy men from the West Indies, (Emeville et al., 2013), men from fertility clinics (Ferguson et al., 2012; Vitku et al., 2016), young Swedish men from the general population, (Richthoff et al., 2003), men exposed to high levels of POPs through fish consumption (Hagmar et al., 2001; Persky et al., 2001), and men living in Norway (Haugen, 2011). Similarly, there were no associations of in utero exposure to PCBs with adult FSH or LH (Vested, 2014). In contrast, among Inuits and several European cohorts, there were positive associations of PCB 153 with LH in some but not all cohorts (Giwercman et al., 2006). Among men with occupational exposures to PCBs at a capacitor manufacturing plant there was an inverse association of dioxin like PCBs with LH of borderline significance (Persky et al., 2012). In another study of occupationally exposed men, TCDD was significantly and positively associated with FSH and LH (Sweeney et al., 1997). In the Faroe Islands, among men with a large range of exposure, PCBs were positively associated with LH but not FSH (Petersen et al., 2018). Variations in associations of

Table 5
Modification of associations of PCBS, dioxins and furans with gonadatropins by CRP and BMI[a].

Gonadotropin	POP	Percentile of CRP or BMI	Conditional association of gonadotropin and POP at CRP percentile[b]		Conditional association of gonadotropin and POP at BMI percentile[b]	
			effect	95% CI	effect	95% CI
LH	∑PCBs	25th	na[c]		0.9	−9.6, 12.6
		75th	na		−13.0	−21.9, −3.2
FSH	∑PCBs	25th	3.8	−5.7, 14.1	5.4	−4.4, 16.2
		75th	−8.2	−16.5, 0.9	−9.4	−17.6, −0.3
LH	∑NDL PCBs	25th	3.1	−7.1, 7.4	na	
		75th	−13.7	−22.1, −4.4	na	
LH	∑MO PCBs	25th	−7.2	−14.7, 1.0	na	
		75th	−14.5	−22.6, −5.5	na	
FSH	∑MO PCBs	25th	−4.8	−11.8, 2.8	na	
		75th	−11.4	−19.1, −3.1	na	
LH	∑DL PCBs	25th	−0.1	−10.9, 11.9	1.0	−11.2, 14.7
		75th	−13.0	−21.7, −3.5	−13.2	−22.1, −3.3
FSH	∑DL PCBs	25th	4.0	−5.9, 15.0	na	
		75th	−10.0	−17.9, −1.3	na	
FSH	∑TEQs	25th	4.5	−10.6, 22.1	3.0	−9.3, 17.0
		75th	−12.9	−22.7, −1.9	−15.7	−25.2, −4.9
LH	∑CA PCBs	25th	0.8	−12.1, 15.6	3.0	−5.5, 12.2
		75th	−18.1	−27.3, −7.6	−10.4	−18.3, −1.8
FSH	∑CA PCBs	25th	7.8	−4.6, 21.8	6.0	−1.7, 14.3
		75th	−12.3	−21.2, −2.3	−9.4	−16.2, −2.0
FSH	∑WA PCBs	25th	4.5	−5.6, 15.7	7.8	−3.6, 20.6
		75th	−9.3	−17.5, −0.3	−10.6	−18.8, −1.7
LH	∑CE PCBs	25th	1.8	−7.1, 11.6	na	
		75th	−21.5	−20.1, −4.2	na	
LH	∑WE PCBs	25th	2.7	−8.4, 15.1	na	
		75th	−31.1	−22.0, −3.1	na	

NDL = non-dioxin-like PCBs; MO = mono-*ortho* PCBs; DL = dioxin-like PCBs; CE=Cooke estrogenic PCBs; WE=Wolff estrogenic PCBs; CA=Cooke anti-estrogenic PCBs; WA=Wolff anti-estrogenic PCBs.

[a] Models adjusted for age, BMI, and lnlipids.

[b] Conditional associations are shown for significant interaction terms ($p < 0.05$) and can be interpreted as the percent change in the gonadotropin with a doubling in POPs exposure at the indicated level of the effect modifier.

[c] na = not applicable since interaction term p-value>0.05.

POPs with gonadotropins could be indicative of gender differences or a threshold of bioavailable estrogen necessary for impacts on circulating hormones. Further, the effect of mixtures of PCBs, PCDDs, and PCDFs might be additive or antagonistic, depending on the population, dose, mixture components and endpoints.

Surprisingly, we found that anti-estrogenic and/or dioxin-like POP groupings were negatively associated with LH. The literature has shown, among multiple factors that contribute to LH secretion, that estrogen plays an important role by exerting feedback to the pituitary in the normal functioning of the HPG axis (Clarke, 2002; Christian et al., 2005); however, the mechanism by which estrogen controls these events has not been delineated. Because control of FSH secretion is more complex than LH and includes stimulus by inhibins and activins, LH has been thought by some to be a better marker for estrogen-negative feedback control of gonadotropin secretion although there is debate on this issue. (Weiss et al., 2004; Cosma et al., 2008; Shaw et al., 2010). In our primary analyses in this study, associations were stronger for LH than FSH.

Because the 1999–2002 NHANES data sets do not provide measurements of other estrogen-related hormones for women, it is difficult to postulate potential mechanisms. Dioxins and related compounds that bind to the AhR are generally thought to elicit anti-estrogenic responses (Safe et al., 1998). The findings of associations between anti-estrogenic and/or dioxin-like POP groupings with LH appear counterintuitive, given that LH levels were decreased, which implies an estrogenic effect. However, our findings may be consistent with previous research suggesting cross-talk between the estrogen receptor and the AhR signaling pathways (Cooke et al., 2008; Swedenborg and Pongratz, 2010). Further, dioxin-likeand potentially anti-estrogenic PCBs have been associated with increased gene expression of estrogen receptor beta and CYP19 coding for aromatase, an enzyme involved in estrogen synthesis (Warner et al., 2012). Inverse relationships of dioxin-like compounds and LH could also reflect direct inhibition of LH synthesis and/or release from the pituitary (Cao et al., 2011; Taketoh, 2007).

4.2. Effect modification

Inverse associations of anti-estrogenic and/or dioxin-like PCB groupings with FSH and LH in the present study were stronger in postmenopausal participants with higher BMI. There is evidence that body composition may play an important role in steroid hormones and SHBG concentrations. In general, the aromatization of androstenedione to estrone in adipose tissue correlates positively with weight (Bulun and Simpson, 1994). Inverse correlations have also been reported between BMI and SHBG for postmenopausal women, resulting in increased bioavailable estradiol (Cauley et al., 1989).

Inverse associations of POPs with LH and FSH were larger in postmenopausal women with higher CRP levels. Some investigators have suggested that PCBs may act through increased inflammatory responses (Hennig et al., 2002). C-reactive protein is a general marker of systematic inflammation and in the current study, CRP was associated with antidiabetic medication use, and higher BMI and triglycerides after adjusting for potential confounders (data not shown). Several studies have also noted associations of CRP with factors relating to estrogen status, including higher levels of estradiol and lower levels of SHBG (Stork et al., 2008; Maggio et al., 2011), as well as stimulation of aromatase Zhao et al. (1996).

4.3. Limitations and strengths

The present investigation has a number of limitations including a small sample size that may have decreased our ability to identify significant associations of POPs with gonadotropins. The cross-sectional design of the study does not allow us to establish a temporal relationship of POP exposures with changes in gonadotropin levels. We adjusted for age, BMI, and lipids, but there may be other important potential confounders for which we have not controlled. Additional congener measurements for complete congener groupings might have helped to better elucidate mechanisms related to associations between PCB groupings and hormones. Estrogenic and anti-estrogenic classes of PCB congeners can express diverse and sometimes conflicting effects (Warner et al., 2012). Finally, the findings might be due to chance, as multiple comparisons were made in the statistical analysis. We did not adjust for multiple comparisons; however, the purpose of these exploratory analyses was to inform and guide future research that could be subject to further rigorous testing (Goldberg et al., 2011).

Despite the limitations, this study has several strengths. To our knowledge, only one other study has evaluated the association of POPs with gonadotropins in postmenopausal women (Persky et al., 2011). The consistency of our findings with that study suggest that our results are not due to chance alone. The use of continuous data ensured that we did not further limit the power of our analysis. Finally, the consistency among multiple exposures groupings with control for confounders support the biologic plausibility of our results.

5. Conclusion

In this investigation, we found significant and borderline significant inverse associations of anti-estrogenic and/or dioxin-like PCB groupings, but not non dioxin-like PCBs, with LH in postmenopausal women, with stronger associations in participants with elevated CRP or BMI. Although not statistically significant in the overall analyses, PCBs were also inversely associated with FSH in the effect modification analysis, with stronger inverse associations in women who were with greater BMI or CRP levels. Adiposity primarily impacted associations of gonadotropins with dioxin-like and anti-estrogenic POPs. Additional studies will be important in delineating specific effects of POPs on sex hormone homeostasis in postmenopausal women.

Credit author Statement

Anissa Lambertino: conceptualization, methodology, formal analysis, writing-original draft, **Victoria Persky:** conceptualization, methodology, writing-reviewing and editing, **Sally Freels:** methodology, formal analysis, writing-reviewing and editing, **Henry Anderson:** writing-reviewing and editing , **Terry Unterman:** writing-reviewing and editing , **Saria Awadalla:** writing-reviewing and editing , **Mary Turyk:** conceptualization, methodology, formal analysis, writing-reviewing and editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Funding from the National Institutes of Health/National Institute of Environmental Health Sciences, grant P30ES027792 Chicago Center for Health and Environment (CACHET). A. Lambertino was supported in part by the National Institute for Occupational Safety and Health training grant T42/OH008672.

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