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Persistent organochlorine pollutants and menstrual cycle characteristics

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Abstract

An evolving body of evidence suggests an adverse relation between persistent organochlorine pollutants (POPs) and menstruation, though prospective longitudinal measurement of menses is limited and served as the impetus for study. We prospectively assessed the relation between a mixture of persistent organochlorine compounds and menstrual cycle length and duration of bleeding in a cohort of women attempting to become pregnant. Eighty-three (83%) women contributing 447 cycles for analysis provided a blood specimen for the quantification of 76 polychlorinated biphenyls and seven organochlorine pesticides, and completed daily diaries on menstruation until a human chorionic gonadotropin confirmed pregnancy or 12 menstrual cycles without conception. Gas chromatography with electron capture detection was used to quantify concentrations (ng g^{-1} serum); enzymatic methods were used to quantify serum lipids (mg dL^{-1}). A linear regression model with a mixture distribution was used to identify chemicals grouped by purported biologic activity that significantly affected menstrual cycle length and duration of bleeding adjusting for age at menarche and enrollment, body mass index, and cigarette smoking.

A significant 3-d increase in cycle length was observed for women in the highest tertile of estrogenic PCB congeners relative to the lowest tertile ($\beta = 3.20$; 95% CI 0.36, 6.04). A significant reduction in bleeding (<1 d) was observed among women in the highest versus lowest tertile of aromatic fungicide exposure ($\gamma = -0.15$; 95% CI −0.29, −0.00). Select POPs were associated with changes in menstruation underscoring the importance of assessing chemical mixtures for female fecundity.

Keywords

Fecundity; Menstruation; Organochlorinated pesticides; Persistent organochlorine pollutants; Polychlorinated biphenyls

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1. Introduction

Female fecundity is defined as the biologic capacity for reproduction irrespective of pregnancy intentions (Buck Louis, 2011), and is speculated to be on the global decline though with limited empirical evidence (Lutz et al., 2003; te Velde et al., 2010). Some authors have suggested a role for endocrine disrupting chemicals such as persistent organochlorine pollutants (POPs) while other authors point to changes in lifestyle for recent birth cohorts (Sallmen et al., 2005). While firm answers remain lacking, an evolving body of evidence suggests an adverse relation between environmental chemicals and a spectrum of fecundity and fertility endpoints as recently summarized (Toft et al., 2004; Buck Louis et al., 2006; Mendola and Buck Louis, 2010).

Regular menstruation has long been used as a proxy of female fecundity, as evident by its cyclic role in preparing for blastocyst implantation or endometrial sloughing in the absence of pregnancy. Animal and primate evidence suggests that organochlorine compounds affect steroidogenesis and hormone levels manifesting in altered menstrual cycles including longer lengths (Barsotti et al., 1976; Bryce et al., 2000; Wojtowicz et al., 2001). Changes in progesterone and estradiol, hormones that control the reproductive endocrine system, have been associated with higher concentrations of dichloro-diphenyl-dichloroethylene (DDE) in women (Windham et al., 2005; Perry et al., 2006). The biologic activity of some POPs including polychlorinated biphenyls (PCBs) and DDE have been studied, and are reported to exert various effects including (anti)estrogenic and/or (anti)androgenic induced changes underscoring the importance of their study for female fecundity.

Menstruation is informative not only in relation to female fecundity, but also with regard to women's health across the lifespan. For example, irregular cycles are associated with fecundity impairments (Jensen et al., 1999), gynecologic disorders such as endometriosis (Treloar et al., 2010), breast cancer (Whelan et al., 1994), and hip fractures (Cooper and Sandler, 1997). Thus, menstruation can be viewed as a proxy of female fecundity and later onset disease risk. Despite such recognition, there remains a scant body of empirical evidence regarding POPs and menstruation as summarized in Table 1. Early epidemiologic studies focusing on POPs and menstruation relied upon fish consumption from environmentally contaminated water bodies as a proxy for exposure and reported reductions in cycle length by 1 d or less (Mendola et al., 1997; Axmon et al., 2004). Recent studies suggest that menstrual cycles may be lengthened by approximately a day or less among women with the highest serum concentrations of TCDD (Eskenazi et al., 2002), select PCB congeners (Cooper et al., 2005) and DDE (Chen et al., 2005) in comparison to women with the lowest concentrations. Of note is a 4 d reduction in cycle length for women in the highest quartile of DDT/DDE relative to the lowest in a small cohort study that utilized daily diaries to capture two menstrual cycles (Windham et al., 2005). Moreover, this study noted that the luteal phase was reduced in relation to DDE and DDT concentrations.

Synthesis of the available evidence regarding the relation between POPs and menstruation is challenging, given three key methodologic issues underlying this avenue of research. The first issue is the considerable heterogeneity in cycle lengths both within and across women

(Liu et al., 2004; Mikolajczyk et al., 2010). Use of self reported menstruation might ignore this issue as reflected in frequently reported digit preferences for length such as 28- and 30-d cycles (Small et al., 2007). The second consideration is the poor validity and reliability of self reported menstrual data in relation to prospectively observed data (Small et al., 2007; Jukic et al., 2008). Lastly, much of the available provocative literature is restricted to analysis of a few POPs despite the mixtures to which humans are exposed. We designed a prospective study in response to these considerations to assess a mixture of serum POPs and menstrual cycle length and duration of bleeding among women discontinuing contraception for the purposes of becoming pregnant.

2. Materials and methods

2.1. Study design and cohort

A prospective cohort design was utilized to recruit 99 women aged 18–44 years who were discontinuing contraception for purposes of becoming pregnant and with no known infertility history. This cohort resided in counties along Lakes Erie and Ontario and was a subset of a larger angler cohort whose aim was to delineate fish consumption patterns and knowledge of advisories. Women were followed until a human chorionic gonadotropin (hCG) confirmed pregnancy or up to 12 menstrual cycles at risk for pregnancy. Complete exposure and menstruation data for all prospectively observed cycles were available for 83 women who contributed 447 cycles for analysis. Full human subjects' approval was given for the conduct of this study, and all women were given an informed consent prior to participation. A more complete description is given elsewhere (Buck Louis et al., 2009).

2.2. Data collection

Women were interviewed upon enrollment regarding their medical and reproductive histories and lifestyle behaviors in the past 12 months before attempting to become pregnant. Research nurses obtained height and weight, instructed women in the fertile window and use of home pregnancy test kits capable of detecting ≤50 m IU of hCG, and completion of daily diaries. Specifically, women recorded acts of sexual intercourse, bleeding and select lifestyle behaviors such as cigarette smoking on a daily basis. A standardized ordinal level bleeding prompt was provided in the diary: none, spotting, light, moderate, and heavy. Menstruation was defined as any report of spotting or bleeding that was followed within 1 d by at least two additional days of bleeding or spotting regardless of intensity in keeping with the established literature requiring menses to vary in intensity for a specific number of days to differentiate it from episodic bleeding (Mikolajczyk et al., 2010). Menstrual cycle length was defined as the prospectively observed interval (in days) between the first day of menstrual bleeding to the next first day of menstrual bleeding. The daily number of cigarettes smoked, caffeinated and alcoholic beverages consumed were summed and standardized to a 28-d cycle to permit comparison of cycles, which varied within and across women depending upon the time required for pregnancy.

2.3. Toxicologic analysis

Upon completion of the interview and diary instruction, ≈25 cc of non-fasting blood was collected. Serum samples were analyzed in batches of 10 along with four quality control

samples (i.e., reagent blank, serum blank, quality control sample containing 15 calibration standards at known values, and a participant's duplicate sample) using gas chromatography with electron capture detection (GC–ECD) as previously described (Greizerstein et al., 1997; Bloom et al., 2007). Limits of detection (LOD) were determined as three standard deviations of 6–10 reagent blanks included in sample batches analyzed. Serum concentrations for select POPs were reported back to cohort participants with no untoward effects stemming from the diffusion of such information (Buck et al., 2010).

Our POP exposures included seven organochlorine pesticides (OCPs) and 76 PCB congeners including 64 single and 12 di-eluting congeners. OCPs or their metabolites included: aldrin, β-hexachlorocyclohexane (β-BHC), dichloro-diphenyl-dichloroethylene (DDE), hexachlorobenzene (HCB), mirex, oxychlor, and *t*-nonachlor. OCPs were subsequently categorized by chemical activity: (1) chlorinated insecticides (β-BHC and DDE); (2) cyclodiene insecticides (aldrin, mirex, oxychlor, and *t*-nonachlor); and (3) aromatic fungicides (HCB).

PCB congeners were summed as a simple total and grouped by purported biologic activity: (1) sum of estrogenic congeners 4 + 10, 5 + 8, 15 + 17, 18, 31, 44, 47, 48, 52, 70, 99, 101, 136, 153, and 188; (2) sum or anti-estrogenic congeners 77 + 110, 105, 114, 126, 171 + 156 and 169; and (3) sum of other remaining congeners (Cooke et al., 2001). Total serum lipids (TL) were quantified using enzymatic methods as the function of total cholesterol (TC), free cholesterol (FC), triglycerides (TG) and phospholipids (PL) and expressed in mg dL^{-1} (Phillips et al., 1989). All observed serum PCB and OCP concentrations were used without substitution for values below the limits of detection (LOD) and were expressed in ng g^{-1} serum (equivalent to parts per billion) to avoid potential biases associated with substitution and lipid standardization practices (Richardson and Ciampi, 2003; Schisterman et al., 2005, 2006).

2.4. Statistical analysis

Descriptive analyses included assessing missing toxicologic or prospective data followed by the distributions of chemical exposures and menstrual cycles. POPs were categorized in tertiles by purported biologic or chemical groupings with the lowest tertile serving as the referent group in all analyses. DDE was categorized in tertiles as well. Means were estimated along with medians and inter-quartile ranges (IQRs), given our expectation for a range of exposure and distributions that were not normally distributed. Given the hierarchical data structure, we first analyzed the cohort using women as the unit of analysis ($n = 83$) then cycles as the unit of analysis ($n = 447$). Women were the relevant unit for assessing baseline characteristics and lifestyle behaviors. Cycle level information averaged over all prospectively observed cycles to estimate summary statistics. This step was to help inform covariate selection for the final analytic models. Average cycle length was subsequently categorized as short (≤24 d), average (25–31 d) or long (≥32 d) based on previous prospective studies (Kolstad et al., 1999; Small et al., 2007). Seventy women contributed 391 cycles with bleeding information. Duration of bleeding was assessed continuously and dichotomized as 1–3, 4–6 and ≥6 d. When estimating mean menstrual cycle length and bleeding duration, we restricted the cohort to women with at least one

complete menstrual cycle that was prospectively observed (n = 70). For women becoming pregnant in the first cycle who did not contribute one fully observed menstrual cycle (n = 13), we used last menstrual period reported at enrollment and the day of the first positive pregnancy test which was to be conducted on the day menses was expected by the woman to estimate cycle length for these few cycles. Bleeding duration could not be estimated for women becoming pregnant in the first cycle given the absence of its reporting.

Using menstrual cycles as the unit of analysis, we used the mixture distribution model (Guo and Manatunga, 2006) to assess the relation between POPs and menstrual cycle length (n = 83 women contributing 447 cycles for analysis). We used a generalized linear model with Poisson link using a generalized estimating equations approach for duration of bleeding (n = 70 women contributing 391 cycles for analysis). We added potential confounders that were *a priori* determined based upon the literature. These models included age at enrollment and at menarche (years), body mass index (BMI weight in kg/height in meters squared and left continuous), and smoking while attempting pregnancy (yes/no), given their reported effects on menses (Harlow and Matanoski, 1991; Kato et al., 1999). We did not include serum lipids, given the lack of association with menstrual cycle length or duration of bleeding. This mixture model comprises both linear regression and log-linear models, which assume a normal and log-Weibull error distribution, respectively. The linear model is used for the analysis of cycle lengths up to an empirical cut-point that we observed to be 47 d, while the log-linear model analyzes the 5% of cycles beyond this cut-point. As such, the mixture model is an informative based approach that permits analysis of all cycles in the cohort rather than restricting to specific cycle lengths or ignoring long cycles. Models for chemical groupings were individually run consistent with our aim to identify chemical signals that may be informative for female fecundity and menstruation.

3. Results

This prospective cohort comprised mostly white married women with largely a college education as previously described (Buck Louis et al., 2009). The distribution of the 447 cycles used in the analysis among the 83 participating women was: 13 women contributed <1 cycle while 17 women contributed 1 cycle, 9 contributed 2 cycles, 7 contribute 3 cycles, 6 contributed 4 cycles, 5 contributed 5 cycles, 5 contributed 6 cycles, and 21 women contributed ≥7 cycles for analysis. With regard to average cycle length across all prospectively observed cycles, 11% of women had ≤24 d cycles while 47% had length between 25–31 d and 42% had lengths ≥32 d. No significant differences were observed for average cycle length by select sociodemographic, reproductive history, BMI, bleeding duration, or lifestyle behaviors while attempting pregnancy as shown in Table 2.

Serum total, estrogenic and anti-estrogenic PCB groupings did not significantly differ by average cycle length as evident by similar means, medians and overlapping IQRs (Table 3). The sum of “other PCB grouping” did significantly ($p < 0.05$) vary by cycle length with the suggestion of a higher percentage of women in the upper tertile having longer cycles compared with the referent group. However, only slight differences were observed for means, medians or IQR. Serum lipids did not significantly vary by average cycle length or duration of bleeding (data not shown). With regard to OCPs, only the cyclodiene

insecticides significantly ($p < 0.05$) varied by average cycle length with a suggestion that women in the highest tertile had longer lengths in comparison to women in the lower tertiles (Table 4).

Table 5 presents the analytic results using prospectively observed cycles as the unit of analysis to estimate the effect (in days) of POPs on menstrual cycle length and duration of bleeding. Specifically, the β-coefficient denotes an increase (positive coefficient) or decrease (negative coefficient) in the average menstrual cycle length or bleeding duration, as measured in number of days. Estrogenic PCBs significantly increased cycle length by approximately 3 d even after adjusting for potential confounders ($\beta = 3.20$; 95% CI 0.36, 6.04). While other point estimates (β coefficients) for the upper tertiles of anti-estrogenic and other PCBs tended to be positive suggestive of a longer effect, none achieve significance. Of note is the reduction in cycle length for the highest tertile of chlorinated insecticides ($\beta = -0.18$; 95% CI −4.11, 3.75) and aromatic fungicides ($\beta = -2.45$; 95% CI −5.95, 1.04) relative to the lowest in adjusted models. A similar reduction was observed for the highest tertile of DDE ($\beta = -0.71$; 95% CI −4.85, 3.43). While the highest tertile of OCP exposure was associated with a reduction in bleeding duration, the effect was only significant for aromatic fungicides (HCB) ($\gamma = -0.15$; 95% CI −0.29, −0.002).

4. Discussion

Our findings that menstrual cycle length is affected by select POPs is intriguing, particularly given that PCB groupings tended to be associated with a longer cycle while the OCPs with a shorter cycle. Of all the PCB groupings assessed, only the purported estrogenic PCBs significantly prolonged menstruation by an average of approximately 3 d even after adjusting for potential confounders. The confidence interval suggests that the effect may be slightly more than 1 d to 7 or more days underscoring the inherent variability of this point estimate. No clear pattern emerged when assessing PCB groupings and duration of bleeding as bi-directional effects were observed. While OCPs tended to be associated with a reduction in cycle length and duration of bleeding, only the relation between aromatic fungicides (HCB) and bleeding duration achieved significance. Specifically, bleeding was reduced by approximately three-quarters of a day for women in the highest tertile relative to the lowest.

To our knowledge, this is one of the first prospective cohort studies that quantified a mixture of serum POP concentrations for women not using any hormonal medications and with longitudinally measured menstruation and lifestyle factors such as smoking reported to affect menstruation (Kritz-Silverstein et al., 1999). Our finding for a longer menstrual cycle by approximately 3 d for women in the highest tertile of estrogenic PCBs is intriguing and consistent with similar increases observed for other endocrine disrupting chemical such as TCCD, DDT/DDE, and PCBs (Eskenazi et al., 2002; Chen et al., 2005; Cooper et al., 2005; Chao et al., 2007; Toft et al., 2008). Despite these earlier studies relying upon self reported menstruation histories, our finding based upon prospectively observed menstruation corroborates these earlier findings and may explain the smaller observed effect on cycle length relative to our larger effect (<1 versus ≈3 d, respectively). Our finding is inconsistent with the first reported cohort study to assess 10 PCB congeners and four OCPs in relation to

prospectively observed menstruation for two cycles (Windham et al., 2005). While PCBs conferred no significant effect, DDT/DDE reduced cycle length by 4 d, an effect size comparable to ours for estrogenic PCBs. However, after adjusting for potential confounders, the effect size was reduced to <1 d. In our cohort, serum DDE also was associated with a reduction in cycle length with the upper bound of the confidence interval approaching 3 d. However, this finding did not achieve significance.

To date, there is little evidence that POPs affect duration of bleeding with the exception of a reduction of approximately 1 d among 33 girls aged 13–19 years whose mothers had PCB and PCDF exposure as reported to the Yucheng registry (Yang et al., 2005). We observed no clear relation between PCBs and duration of bleeding, though HCB significantly reduced bleeding by approximately <1 d. To our knowledge, this is the first reported decrement in bleeding associated with women's serum HCB concentrations. Given women's narrow range for bleeding durations, sufficiently powered cohorts may be required to detect small changes in bleeding duration.

The etiologic mechanisms underlying the relation between POPs and menstrual cycle length and duration of bleeding are speculative at best. Recently reported findings from prospective cohort studies offer insight into underlying mechanisms, particularly the role of reproductive hormones governing the ovarian and menstrual cycles. Windham and colleagues (2005) reported that serum DDT/DDE shortened the luteal phase by approximately 1.5 d. Moreover, an inverse relation was observed between serum DDE and progesterone during the luteal phase. A subsequent prospective cohort study of 287 female textile workers aged 20–34 years followed for one year or until pregnant reported that serum DDT was associated with reductions in estrone conjugate (E_1C) and pregnanediol-3-glucuronide (PdG) during the periovulatory and luteal phases of the cycle (Perry et al., 2006). Collectively, these data suggest that POPs may affect cyclic reproductive hormonal milieu resulting in subtle changes in menstrual characteristics such as cycle length, possibly, and duration of bleeding. Our cohort study is limited by the lack of information on reproductive hormones and, therefore, we cannot further assess the interrelated-ness of serum POPs, reproductive hormones and menstruation. Another important limitation is that our chemical models were independently assessed and will await corroboration from larger cohorts powered to considered additional chemical mixtures in the analysis of POP exposures and menses.

When weighing available evidence focusing on the impact of POPs on reproductive outcomes, it is important not to minimize subtle changes in cycle length and/or duration of bleeding. One key reason is the new evidence linking menses with fecundability. For example, Small and colleagues (2011) followed a cohort of 401 women who contributed 3536 cycles for analysis and reported a 51% reduction in the probability of pregnancy each menstrual cycle for women with highly variable cycles relative to women with less variability. The extent to which POPs may be etiologically associated with the variability in menstrual cycle characteristics remains to be established. This is an important avenue of research not only for a clearer understanding of menstrual cycle variation, but its subsequent relation with fecundity and later onset diseases.

5. Conclusion

In sum, this prospective cohort study with longitudinal measurement of menstruation identified estrogenic PCB congeners as being associated with a 3-d increase in cycle length, and HCB with a <1 reduction in duration of bleeding among prospectively observed menstrual cycles.

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Abbreviations

β-BHC	β-hexachlorocyclohexane
DDE (p,p′-DDE)	dichloro-diphenyl-dichloroethylene
DDT	dichlorodiphenyltrichloroethane
EDCs	endocrine-disrupting chemicals
FC	free cholesterol
GC–ECD	gas chromatography with electron capture detection
HCB	hexachlorobenzene
hCG	human chorionic gonadotropin
LOD	limits of detection
OCPs	organochlorine pesticides
PCBs	polychlorinated biphenyls
PL	phospholipids
TC	total cholesterol
TG	triglycerides
TL	total serum lipids
CI	confidence interval

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Table 1

Persistent organochlorine pollutants and menstruation – weight of evidence.

References	Design	Study population (sample/cohort size)	Exposure	Measuring menstruation	Largest cycle effect[a] (change in days)
Proxy exposure					
Mendola et al. (1997)	Cross-sectional	Reproductive age women (n = 2223)	Fish consumption	Self reported	↓ (1.11)
Axmon et al. (2004)	Cross-sectional	Reproductive age women (n = 941)	Fish consumption	Self reported	↓ (0.46)
Individual exposures					
Eskenazi et al. (2002)	Retrospective cohort	Women <40 years (n = 301)	Serum TCDD	Self reported	↑ (0.93) for premenarcheal exposure
Chen et al. (2005)	Cross-sectional	Women aged 20–24 years (n = 47)	Serum DDT, DDE	Self reported	↑ (0.66)
Cooper et al. (2005)	Cross-sectional	Pregnant women (n = 2314)	Serum DDE, PCBs	Self reported	↑ (0.7) PCBs
Windham et al. (2005)	Prospective cohort	Women aged 18–40 years (n = 49)	Serum 10 PCBs, 4 OCPs and DDT/DDE	Daily diaries and urines	↓ (4) DDT/DDE
Ouyang et al. (2005)	Cross-sectional	Textile workers aged 20–34 years (n = 466)	Serum DDT and metabolites	Self reported	↓ Odds of short (<21 d) cycle
Yang et al. (2005)	Prospective cohort	Girls aged 13–19 years (n = 33)	Maternal Yucheng registry	Bleeding diaries for 84 d	↓ (1) Bleeding duration
Chao et al. (2007)	Cross-sectional	Women (29 ± 4.6 years) giving birth (n = 119)	Placental PCB–TEQ	Self reported length	+Association for cycles >33 d
Toft et al. (2008)	Cross-sectional	Pregnant women from 4 countries (n = 1494)	Serum PCB 153 and DDE	Self reported	↑ (0.1) for DDE

↓ Denotes reduction in menstrual cycle length; ↑ denotes increase in menstrual cycle length.

DDE (p,p′-DDE), dichloro-diphenyl-dichloroethylene.

DDT, dichlorodiphenyltrichloroethane.

E_1C, estrone conjugate.

OCPs, organochlorine pesticides.

PCBs, polychlorinated biphenyls.

PCDF, polychlorinated dibenzo furans.

PdG, pregnanediol-3-glucuronide.

TCDD, 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin.

TEQ, dioxin toxic equivalents.

OCPs, organochlorine pesticides.

PCBs, polychlorinated biphenyls.

PCDF, polychlorinated dibenzo furans.

PdG, pregnanediol-3-glucuronide.

TCDD, 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin.

TEQ, dioxin toxic equivalents.

[a]Represents the largest observed effect irrespective of significance.

Table 2

Study cohort by observed averaged menstrual cycle length (n = 83).

Characteristic	Short cycles ≤24 d (n = 9) n (%)	Average cycles 25–31 d (n = 39) n (%)	Long cycles ≥32 d (n = 35) n (%)
Age (in years)			
20–29	6 (67)	11 (28)	16 (46)
30–34	3 (33)	28 (72)	19 (54)
Mean (±SD)	28.9 (3.4)	30.6 (2.2)	29.7 (2.3)
Education			
High school	1 (11)	4 (10)	4 (11)
College/graduate	8 (89)	35 (90)	31 (89)
Age at menarche (years)			
≤10	0 (0)	3 (8)	1 (3)
11–12	1 (11)	14 (36)	8 (23)
≥13	8 (89)	22 (56)	26 (74)
Mean (±SD)	13.2 (1.3)	12.8 (1.6)	13.4 (1.4)
Gravidity (# pregnancies)			
0	1 (11)	10 (26)	9 (26)
≥1	8 (89)	29 (74)	26 (74)
Mean (±SD)	1.6 (0.7)	1.4 (1.2)	1.2 (0.9)
Parity (# births)			
0	2 (22)	12 (31)	11 (31)
≥1	7 (78)	27 (69)	24 (69)
Mean (±SD)	1.0 (0.7)	0.9 (0.7)	0.9 (0.7)
BMI (weight in kg height^{-1} in m[2])			
Under-weight (<18.5)	0 (0)	3 (8)	1 (3)
Normal (18.5–24.9)	6 (67)	24 (61)	21 (60)
Over-weight (≥25.0)	3 (33)	12 (31)	13 (37)
Mean (±SD)	26.5 (6.3)	23.2 (4.5)	24.7 (5.5)
Duration of bleeding (# days)[a]			
1–3	2 (29)	1 (3)	1 (3)
4–5	3 (42)	12 (34)	10 (36)
≥6	2 (29)	22 (63)	17 (61)
Mean (±SD)	3.8 (1.9)	5.8 (1.5)	5.9 (1.6)
Behaviors[b]			
Mean (±SD) cigarettes	17.5 (45.6)	44.7 (108.6)	43.0 (124.0)
Mean (±SD) alcoholic drinks	10.2 (19.2)	10.7 (11.5)	7.3 (11.1)
Mean (±SD) caffeine beverages	37.0 (27.6)	40.5 (32.4)	50.6 (39.1)

Note: None of the above differences achieved significance.

[a] Bleeding duration restricted to women with one prospectively observed cycle.

[b] Obtained from daily diaries and standardized to a 28-d cycle.

Table 3

Serum polychlorinated biphenyl concentrations by observed averaged menstrual cycle length (n = 447 cycles).

PCB groupings – tertiles (ng g^{-1} serum)	Short cycles ≤24 d (n = 9) n (%)	Average cycles 25–31 d (n = 39) n (%)	Long cycles ≥32 d (n = 35) n (%)
Σ Total PCBs			
1st (3.55–4.97)	4 (44)	12 (31)	10 (28)
2nd (4.98–5.66)	5 (56)	15 (38)	9 (26)
3rd (5.67–12.63)	0 (0)	12 (31)	16 (46)
Mean (±SD)	4.9 (0.6)	5.5 (1.2)	5.7 (1.7)
Median (IQR)	5.0 (4.8, 5.3)	5.2 (4.7, 6.0)	5.2 (4.9, 6.2)
Σ Estrogenic PCBs[a]			
1st (1.64–2.15)	4 (44)	12 (31)	9 (26)
2nd (2.16–2.38)	4 (44)	15 (38)	10 (28)
3rd (.39–4.54)	1 (12)	12 (31)	16 (46)
Mean (±SD)	2.1 (0.3)	2.4 (0.6)	2.4 (0.6)
Median (IQR)	2.2 (1.9, 2.3)	2.3 (2.1, 2.8)	2.3 (2.1, 2.6)
Σ Anti-estrogenic PCBs[b]			
1st (0.03–0.16)	4 (45)	11 (28)	12 (34)
2nd (0.17–0.21)	3 (33)	8 (21)	14 (40)
3rd (0.22–0.65)	2 (22)	20 (51)	9 (26)
Mean (±SD)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)
Median (IQR)	0.2 (0.1, 0.2)	0.2 (0.2, 0.3)	0.2 (0.1, 0.2)
Σ Other PCBs[c]			
1st (1.87–2.57)	2 (22)	12 (31)	11 (31)
2nd (2.58–2.98)	7 (78)	15 (38)	8 (23)
3rd (2.99–8.49)	0 (0)	12 (31)	16 (46)
Mean (±SD)	2.6 (0.3)	2.8 (0.6)	3.1 (1.1)
Median (IQR)	2.7 (2.6, 2.8)	2.7 (2.4, 3.2)	2.8 (2.5, 3.3)

Note: None of the above differences achieved significance.

IQR, inter-quartile range.

Σ, sum.

[a] Includes of PCB congeners 4 + 10, 5 + 8, 15 + 17, 18, 31, 44, 47, 48, 52, 70, 99, 101, 136, 153, 188.

[b] Includes PCB congeners 77 + 110, 105, 114, 126, 171 + 156, 169.

[c] Includes remaining PCB congeners. Groups are significantly different at $p < 0.05$.

Table 4

Serum organochlorine pesticide groupings by observed averaged menstrual cycle length (n = 447 cycles).

Organochlorine pesticide groupings (ng g^{-1} serum)	**Short cycles ≤24 d (n = 9) n (%)**	**Average cycles 25–31 d (n = 39) n (%)**	**Long cycles ≥32 d (n = 35) n (%)**
Aromatic fungicides[a]			
1st (0.02–0.07)	2 (22)	11 (28)	7 (20)
2nd (0.08–0.11)	3 (33)	13 (33)	18 (51)
3rd (0.11–0.26)	4 (45)	15 (39)	10 (29)
Mean (±SD)	0.10 (0.03)	0.10 (0.04)	0.09 (0.03)
Geometric mean	0.10	0.09	0.09
Median (IQR)	0.11 (0.08, 0.13)	0.10 (0.07, 0.12)	0.10 (0.08, 0.12)
Cyclodiene insecticides[b]			
1st (0.01–0.07)	1 (11)	8 (20)	13 (37)
2nd (0.08–0.12)	7 (78)	19 (49)	7 (20)
3rd (0.13–0.40)	1 (11)	12 (31)	15 (43)
Mean (±SD)	0.09 (0.02)	0.11 (0.05)	0.12 (0.08)
Geometric mean	0.09	0.09	0.09
Median (IQR)	0.09 (0.08, 0.10)	0.10 (0.08, 0.14)	0.11 (0.06, 0.16)
Chlorinated insecticides[c]			
1st (0.39–0.82)	3 (33)	12 (31)	12 (34)
2nd (0.83–1.13)	2 (22)	14 (36)	12 (34)
3rd (1.14–3.60)	4 (45)	13 (33)	11 (32)
Mean (±SD)	1.0 (0.4)	1.1 (0.6)	1.0 (0.4)
Geometric mean	1.0	1.0	1.0
Median (IQR)	1.0 (0.8, 1.2)	1.0 (0.7, 1.5)	0.9 (0.7, 1.2)

IQR, inter-quartile range.

[a] Includes hexachlorobenzene (HCB).

[b] Includes aldrin, mirex, oxychlor, and *t*-nonachlor. Groups are significantly different at $p < 0.05$.

[c] Includes β-BHC and dichloro-diphenyl-dichloroethylene (DDE).

Table 5

Serum organochlorine groupings and observed changes (in days) in menstrual cycle length and duration of bleeding.

Model	Cycle length unadjusted β (95% CI)	Cycle length adjusted β (95% CI)[a]	Bleeding unadjusted γ (95% CI)	Bleeding adjusted γ (95% CI)[a]
Estrogenic PCBs				
1st (1.64–2.15)	Reference	Reference	Reference	Reference
2nd (2.16–2.38)	−0.40 (−4.45, 3.65)	−0.07 (−3.14. 2.99)	0.02 (−0.13, 0.17)	0.02 (−0.14, 0.17)
3rd (2.39–4.54)	3.91 (0.09, 7.73)	3.20 (0.36, 6.04)	0.08 (−0.06, 0.22)	0.06 (−0.09, 0.21)
Anti-estrogenic PCBs				
1st (0.03–0.16)	Reference	Reference	Reference	Reference
2nd (0.17–0.21)	0.41 (−4.37, 5.19)	0.38 (−4.08, 4.84)	−0.05 (−0.21, 0.10)	−0.07 (−0.22, 0.09)
3rd (0.22–0.65)	1.16 (−2.84, 5.16)	1.09 (−3.04, 5.21)	−0.05 (−0.18, 0.09)	−0.09 (−0.24, 0.06)
Other PCBs				
1st (1.87–2.57)	Reference	Reference	Reference	Reference
2nd (2.58–2.98)	−2.39 (−6.35, 1.58)	−2.79 (−6.00, 0.13)	−0.02 (−0.17, 0.12)	−0.03 (−0.19, 0.12)
3rd (2.99–8.49)	2.82 (−1.38, 7.03)	3.23 (−0.69, 7.01)	0.08 (−0.07, 0.23)	0.05 (−0.11, 0.21)
Aromatic fungicides				
1st (0.02–0.07)	Reference	Reference	Reference	Reference
2nd (0.08–0.11)	−1.16 (−4.97, 2.64)	−1.02 (−4.89, 2.85)	0.03 (−0.11, 0.18)	0.06 (−0.09, 0.20)
3rd (0.11–0.26)	−2.83 (−6.49, 0.83)	−2.45 (−5.95, 1.04)	−0.15 (−0.30, 0.00)	−0.15 (−0.29, −0.002)
Cyclodiene insecticides				
1st (0.01–0.07)	Reference	Reference	Reference	Reference
2nd (0.08–0.12)	−1.90 (−5.86, 2.07)	−2.08 (−6.01, 1.85)	−0.07 (−0.21, 0.08)	−0.12 (−0.27, 0.03)
3rd (0.13–0.40)	1.54 (−3.48, 6.57)	1.42 (−2.89, 5.72)	−0.06 (−0.21, 0.10)	−0.11 (−0.26, 0.05)
Chlorinated insecticides				
1st (0.39–0.82)	Reference	Reference	Reference	Reference
2nd (0.83–1.13)	2.09 (−2.49, 6.69)	1.59 (−2.21, 5.38)	0.09 (−0.06, 0.23)	0.07 (−0.09, 0.22)
3rd (1.14–3.60)	0.09 (−4.74, 4.92)	−0.18 (−4.11, 3.75)	−0.00 (−0.15, 0.14)	−0.06 (−0.22, 0.10)
DDE				
1st (0.38–0.81)	Reference	Reference	Reference	Reference
2nd (0.82–1.12)	2.23 (−2.46, 6.92)	1.45 (−2.60, 5.49)	0.10 (−0.04, 0.24)	0.08 (−0.07, 0.23)
3rd (1.13–3.59)	0.10 (−4.70, 4.90)	−0.71 (−4.85, 3.43)	0.01 (−0.14, 0.15)	−0.05 (−0.21, 0.11)

Note: Cycle length analysis based on 447 cycles from 83 women while duration of bleeding was based on 391 cycles from 70 women.

β, change in days of mean standard cycle length; γ log-change in the mean bleeding days.

CI, confidence interval.

[a]Adjusted for age at enrollment and menarche, BMI, and smoking.