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Menstrual cycle perturbation by organohalogens and elements in the Cree of James Bay, Canada

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HIGHLIGHTS

- This is the first detailed study looking at the menstrual cycle characteristic of the Cree women of James Bay, Canada.
- Collinearity in POH and element data was reduced by principal components analysis to a few uncorrelated variables.
- The menstrual cycle characteristics data were bootstrapped to provide a conservative less biased set of response variables.
- After adjusting for confounders a principal component showed significant negative association with cycle length.
- The menstrual cycle function of these women may be altered by exposure to POHs and elements from their environment.

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ABSTRACT

Persistent organohalogens (POHs) and metals have been linked to alterations in menstrual cycle function and fertility in humans. The Cree First Nations people living near James Bay in Ontario and Quebec, Canada, have elevated levels of POHs, mercury and lead compared to other Canadians. The present study examines the interrelationships between selected POHs and elements on menstrual cycle function in these Cree women.

Menstrual cycle characteristics were derived from structured daily diaries and endocrine measurements from daily urine samples collected during one cycle for 42 women age 19–42. We measured 31 POHs in blood plasma and 18 elements in whole blood, for 31 of the participants. POHs and elements detected in ≥70% of the participants were transformed by principal component (PC) analysis to reduce the contaminant exposure data to fewer, uncorrelated PCA variables.

Multiple regression analysis revealed that, after adjusting for confounders, PC-3 values showed significant negative association with cycle length, after adjusting for confounders ($p = 0.002$). PC-3 accounted for 9.2% of the variance and shows positive loadings for cadmium, selenium, and PBDE congeners 47 and 153, and a negative loading for copper. Sensitivity analysis of the model to quantify likely effect sizes showed a range of menstrual cycle length from 25.3 to 28.3 days using the lower and upper 95% confidence limits of mean measured contaminant concentrations to predict cycle length. Our observations support the hypothesis that the menstrual cycle function of these women may be altered by exposure to POHs and elements from their environment.

1. Introduction

The human menstrual cycle is a result of a series of interrelated hormonal changes within the hypothalamic–pituitary–ovarian axis. Epidemiologic studies have shown that subtle changes in the

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hormonal levels during the cycle are associated with disrupted, subfertile or infertile menstrual cycles (e.g., Baird et al., 1999; Brodin et al., 2008). This complex and delicate endocrine interplay of the menstrual cycle is vulnerable to toxicants and contaminants that can act as endocrine disruptors. This nexus of hormonally-active contaminants leading to menstrual cycle changes associated with infertility is compelling (Ouyang et al., 2005; Harley et al., 2010), yet little is known about the association between many specific environmental contaminants and menstrual cycle function.

Persistent organohalogens (POHs) comprise a diverse group of chemicals linked to a number of disorders of reproductive function (Harley et al., 2010; Foster et al., 2008; Mendola et al., 2008). While the pesticide *p,p'*-dichlorodiphenyltrichloroethane (DDT) and its metabolite *p,p'*-dichlorodiphenyldichloroethylene (DDE) was associated with spontaneous abortion and neurodevelopmental delay (Eskenazi et al., 2009), their effects on reproductive health are not clear. Higher levels of DDT are associated with reduced levels of urinary estradiol and progesterone metabolites (Perry et al., 2006). Reports variously describe DDT and DDE exposures to be associated with decreasing (Windham et al., 2005; Ouyang et al., 2005), increasing (Toft et al., 2008), or not affecting (Chen et al., 2005) the length of the menstrual cycle. Windham et al., (2005) observed that DDE levels were also associated with shorter luteal phases and reduced luteal phase progesterone levels. In a pilot study of First Nation Cree, Wainman et al. (2004) reported that mid-follicular phase luteinizing hormone (LH) levels were correlated with total DDE/DDT exposure.

Exposure to polychlorinated biphenyls (PCBs) was associated with shorter menstrual cycles in Swedish fishermen's wives (Mendola et al., 1997; Toft et al., 2008) and lowered success rates of *in vitro* fertilization (Meeker et al., 2011). Compared to controls, women most heavily exposed to PCBs and dibenzofurans in the Yucheng incident were shown to have shorter menstrual cycles and either longer menstrual flow (Yang et al., 2011) or abnormal menstrual flow (Yu et al., 2005). By contrast, Buck Louis et al. (2011) found that women in the highest tertile of exposure to estrogenic PCBs had longer menstrual cycles than the least exposed group. Windham et al. (2005) were unable to find an association between PCB exposure and cycle length or hormone parameters. Wainman et al. (2004) found that in the Cree women of James Bay, urinary estrogen and follicle stimulating hormone (FSH) levels in the luteal phase were correlated with the PCB 138 levels, but the study group was only 9 women. Chao et al. (2010) provided inconclusive evidence that polybrominated diphenyl ether (PBDE) levels in breast milk were associated with longer and irregular menstrual cycles.

Metal exposures may also alter human reproductive health, though their effects on reproductive hormones and the menstrual cycle are not clear. Michos et al. (2010) reported that estrogen levels in eumenorrheic women were directly linked with zinc levels and inversely related to copper levels. Elevated blood levels of lead in women were associated with higher circulating levels of FSH and LH (Krieg, 2007), irregular menstruation, infertility, and elevated serum estradiol levels (Chang et al., 2006). Pollack et al. (2011) looked at the toxic metals cadmium, lead, and mercury and observed decreased FSH with increasing cadmium and increased progesterone with increased lead levels. Jackson et al. (2011) detected a positive relationship between cadmium and early follicular phase estradiol levels. In contrast to Pollack et al. (2011), Jackson et al. (2011) found no relationship between lead and progesterone. Both Pollack et al. (2011) and Jackson et al. (2011) found that mercury levels were not related to reproductive hormone levels, but the levels of mercury, as well as lead and cadmium, were relatively low.

Cree communities on the Ontario west coast and Quebec east coast of James Bay have relatively high levels of POHs, lead, mercury and cadmium, compared to more southern urban populations in Canada (Tsuji et al., 2006, 2008; Dewailly and Nieboer, 2005; Bonnier-Viger, 2007; Nieboer et al., 2011; Charania et al., 2014). While the source of POHs is unknown for these populations, abandoned Mid-Canada Radar Line bases and accumulation within traditional foods are possible sources (Tsuji et al., 2005). Mercury exposure in this population is usually associated with fish consumption (Van Oostdam et al., 1999; Bonnier-Viger, 2007), whereas blood lead in this population has previously been correlated with hunting activities involving leaded ammunition (Tsuji et al., 2008). Cadmium exposure in this group is related to cigarette smoking rather than food (Charania et al., 2014).

In the present study, we further investigated the interrelationships of effects by selected POHs and elements on menstrual cycle characteristics in Cree women from eastern and western James Bay communities. In the current study we did not attempt to determine the source of contaminant exposure. Menstrual cycle function was assessed using diary entries and daily measurements of urinary reproductive hormones or their metabolites.

2. Materials and methods

2.1. Study group

Participants were women from two remote Cree First Nation communities in subarctic Canada. Population sizes (all individuals) in these communities are very limited (Fort Albany 850; Oujé-Bougoumou 622), and all residents between ages 18 and 42 that met study inclusion criteria (Fort Albany 169; Oujé-Bougoumou 137) were approached to participate in the study. Thus, the sample size represents a census of all available participants.

Participants were first recruited primarily through community presentations, and subsequently by personal interviews with community field coordinators. Written consent was obtained from all participants in person by community-based health care coordinators communicating in Cree language or English. This study was approved by the McMaster University Research Ethics Board (Study Number 98–47).

Eligible participants were Cree women between 18 and 42 years old at the time of recruitment, who had not breast fed or used an intrauterine device, oral hormonal contraception or other hormonal replacement/medication for at least 3 months, or injectable hormonal contraception for 12 months. Participants had not been pregnant for at least 6 months, had not had surgery on their ovaries, uterine tubes or uterus and did not have an endocrine disorder (diabetes, thyroid disease, adrenal disease, pituitary disease), reproductive disease (including chronic pelvic inflammatory disease and endometriosis), or cancer of the vagina, cervix, uterus, ovary or bladder. Subjects were not excluded for irregular or absent menstrual periods.

The study was conducted in two phases: a pilot and a larger expanded study. For the pilot study, participants were recruited from Fort Albany, Ontario, on the west shore of James Bay ($n = 9$). For the larger study, 37 participants were recruited from Fort Albany, Ontario, and Oujé-Bougoumou, Quebec, a Cree community located 600 km southeast of Fort Albany and 360 km southeast of James Bay. Participation was from July 2000 through February 2001 for the pilot study, and from February through November 2004 for the larger study. Since four women from Fort Albany participated in both studies, only data from their participation in the larger study were included in the analyses to avoid bias due to multiple observations that are correlated or not independent.

Of the 42 eligible women, complete contaminant exposure measures were obtained for 31 women. Indices of menstrual cycle function were derived from endocrine hormones measured in daily