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Endocrine disrupting chemicals and ovulation: Is there a relationship?

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ABSTRACT

Although the potential for endocrine disrupting chemicals (EDCs) to disrupt female fecundity is great, few studies have assessed the threat to human reproduction. This study investigates levels of organochlorines in relation to their impact on women's menstrual cycles and ovulatory status.

To address concerns of the Akwesasne Mohawk community in upstate New York regarding well-established exposure to EDCs, women's fertility and reproductive health endpoints, we recruited 215 women between the ages of 21 and 38 years to measure menstrual cycle characteristics and levels of local pollutants. Of these, 155 women collected saliva over the course of their menstrual cycle allowing for analysis of estradiol and progesterone levels and the determination of ovulatory status in relationship to their serum pollutant levels. A subset of participants (15) who did not commence cycling within a month of their enrollment were not included in the analysis, hence reducing the sample size to 140 participants. Additionally, a lipid panel, estradiol and progesterone were assessed in serum on Day 3 of the menstrual cycle.

Median cycle length for women in the sample was 29 days. After aligning the cycles, 110 women were considered ovulatory and 45 (29%) anovulatory. Concentrations of groups of more persistent PCBs congeners, HCB, and *p,p'*-DDE did not differ significantly with ovulatory status. However, a sub-group of low-chlorinated PCB congeners, considered to be estrogenic were significantly higher among anovulatory women. These findings suggest that certain EDC's, ubiquitous in our environment, may adversely affect menstrual cycles and thus have the capacity to impair reproductive function, including likelihood of conception.

1. Introduction

Organochlorines, such as polychlorinated biphenyls (PCBs), hexachlorobenzene (HCB), and dichlorodiphenyldichloroethylene (*p,p'*-DDE, a metabolite of DDT), are known to have endocrine disrupting or hormonally active properties. These exogenous compounds and other persistent organic pollutants (POPs), interfere with normal endocrine homeostasis and are related to female fecundity (Buck Louis et al., 2006; Mendola et al., 1997; Sallmen et al., 2005; Toft et al., 2004; Toft, 2014).

Endocrine disrupting chemicals (EDCs) are capable of interfering with normal tissue and organ development (Gore et al., 2015a, 2015b; Skakkebaek et al., 2011). Given the high hormonal sensitivity of reproductive organs, it is biologically plausible that exposure at critical periods of development across the life cycle (i.e. fetal development, perinatal life, childhood, and puberty) to EDCs may result in reproductive dysfunction. EDCs may interfere with female reproduction through multiple pathways (UNEP/WHO, 2015). There are two pathways that seem especially relevant: 1) the capacity of EDCs to alter the structure of female reproductive organs, and 2) the potential for EDCs to disrupt steroid hormone levels and organ function (Gore et al., 2015a, 2015b).

The antiestrogenic, estrogenic, androgenic, or antiadrogenic

Abbreviations: AhR, Aryl hydrocarbon receptor; BMI, Body mass index; CDC, Centers for Disease Control and Prevention; DDT, 2,2-bis(*p*-chlorophenyl)-1,1,1-trichloroethane; *p, p'*-DDE, 2,2-bis(*p*-chlorophenyl)-1,1-dichloroethylene; HCB, Hexachlorobenzene; OR, Odds ratio; PCBs, Polychlorinated biphenyls; POPs, Persistent organic pollutants; TEFs, Toxic equivalent factors; TEQs, Toxic equivalents

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properties of certain specific PCBs are well-documented (Cooke et al., 2001; Pliskova et al., 2005; Ulbrich and Stahlmann, 2004; Wolff et al., 1997), while *p,p'*-DDE appears to have antiandrogenic effects (Kelce et al., 1995; Kjeldsen et al., 2013; Langer et al., 2014; Lichtensteiger et al., 2015). HCB and *p,p'*-DDE have been consistently found in human follicular and reproductive fluids (Jarrell et al., 1993; Trapp et al., 1984). *p,p'*-DDE was positively correlated with failed fertilization in women undergoing in vitro fertilization (Younglai et al., 2002). At low exposure, HCB has been shown to alter morphologic and functional changes in the ovaries of non-human primates (Babineau et al., 1991; Foster et al., 1992), as well as induce anovulatory cycles and suppress estradiol levels (Muller et al., 1978). Ovulatory dysfunction and menstrual cycle disturbances are a frequent cause of subfertility in women, presenting as short, long, irregular or absent menstrual cycles (Rebar, 2014). A lengthening of the menstrual cycle was related to high serum PCB levels in women (Cooper et al., 2005), which can result in longer time-to-pregnancy.

Although preliminary animal and laboratory studies indicate the potential for these chemicals to disrupt female fecundity is great, few studies have examined organochlorines in relation to their impact on women's ovulatory status. Fertility studies among women are not scarce, but often employ small sample sizes (<100) given the participant burden due to the collection protocol. Even low concentrations of EDCs could disturb endocrine regulated processes necessary for the overall function of the female reproductive system, and in particular the ovarian cycle (Buck et al., 1997a, 1997b; Mendola et al., 1995, 1997; Windham et al., 2002; Yu et al., 2000).

We report on the association of specific organochlorines on the ovulatory status of a sample of Native American women exposed to organochlorines due to local environmental pollution. Furthermore, we address the multiple, concomitant exposure to these EDCs on ovulatory status.

2. Methods

2.1. Sample and site characteristics

The Akwesasne Mohawk Nation (AMN) is a sovereign nation situated on the St. Lawrence River with territory adjoining New York State, Ontario and Quebec, Canada. This population is in close proximity to three industrial sites known to have contaminated the St. Lawrence River. Three industrial sites discharged significant quantities of PCBs (primarily Aroclor 1248), into the St. Lawrence River and its three tributaries (Sloan and Jock, 1990). One of these became a National Priority Superfund Site (General Motors Central Foundry Division) and two New York State Superfund Sites (Reynolds Metal Company and Aluminum Company of America) (New York State Department of Environmental Conservation, 2000). The pollution of the local waters lead to some local species of fish, birds, amphibians and mammals to have toxicant levels exceeding the US Food and Drug Administration's tolerance limits for human consumption (Forti et al., 1995; Sloan and Jock, 1990). Fish and wildlife from the river were consumed as part of the typical diet until advisories were issued in the mid-1980's not to consume locally caught fish (Buck et al., 2000; Fitzgerald et al., 1995; Fitzgerald et al., 1998, 2004).

Since the early 1980s, community members of the Mohawk Nation of Akwesasne have had concerns regarding the health ramifications of exposure to environmental contaminants. The initial studies of PCB exposure and health effects began after a Mohawk midwife, Katsi Cook, raised concerns about the safety of breastfeeding due to the presence of toxicants in breastmilk. In addition, for a number of years women have reported to health care providers long times to conception and many early pregnancy losses. At this time, a study among Akwesasne girls provided evidence of an altered rate of sexual maturation in relation to their PCB exposure (Denham et al., 2005). The current study of menstrual cycle characteristics and reproductive endpoints was then initiated in partnership with the St. Regis Mohawk Tribal Health Services. The collaboration was guided by principles of community-based research partnerships that has unfolded between the community at Akwesasne and researchers at the University at Albany as described in much greater detail in other publications (Ravenscroft et al., 2015; Schell and Tarbell, 1998; Schell et al., 2005; Schell et al., 2007).

To address concerns of the Akwesasne Mohawk community in upstate New York regarding women's fertility and reproductive disease endpoints in the context of known PCB exposure, we recruited 215 women between 2009 and 2013, to assess the relationship between environmental toxicants and reproductive function, specifically menstrual cycle characteristics. To be eligible for the project, women were required to be Akwesasne residents and between 21 and 38 years of age. Women could not participate if they were: 1) taking any form of hormonal birth control; 2) pregnant or nursing (though could reapply in 6 months time); and 3) taking any medications for thyroid dysfunction. If the participant missed more than two sequential days of saliva collection during their menstrual cycle, they were asked to start the collection process over at the beginning of their next cycle.

Of the 215 women, 60 eventually withdrew or became ineligible to continue. Three became pregnant and two started thyroid medications and were no longer eligible; 28 women were enrolled but never started the saliva collection protocol, 8 were no longer interested in participating after they completed the interview process and had their blood drawn. Thirty women were asked to restart collection because they missed collecting two days in a row; of these 21 considered the saliva collection protocol too rigorous and decided to withdraw from the project. Nine women completed salivary collection after restarting.

As such, 155 women completed interviews, had their blood drawn for PCB analysis and collected saliva over the course of their menstrual cycle allowing for analysis of daily estradiol and progesterone levels and the determination of ovulatory status. Of these 155 women, 15 enrolled in the project with a history of menstrual irregularity who did not commence cycling within a month of their enrollment. This subset of participants is referred to here as non-cycling women (NCW) and they were not included in the analysis, hence reducing the sample size to 140 participants for analysis. To the best of our knowledge, with the exception of the 15 women with a history of menstrual irregularity, none of these women were actively trying to conceive, had any fertility concerns, or a medical diagnosis of reproductive dysfunction at the start of the project.

2.2. Data collection by interview

Information on sociodemographic characteristics, dietary, reproductive, and menstrual cycle histories were obtained by interviews and questionnaires. Serial saliva samples from women were collected for the analysis of estradiol (E_2) and progesterone (P_4) content following standardized protocols (Lipson and Ellison, 1992, 1994, 1996). Anthropometric measurements (including height, weight, seven skinfolds, three breadths, and five circumferences), were taken in triplicate by two trained data collectors. Body mass index (weight (kg)/height $(m)^2$) was calculated for each woman and classified into adult weight status categories (normal weight, overweight and obese; http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html). All data were collected by project staff who were members of the Akwesasne