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The endocrine and reproductive function of the female Yucheng adolescents prenatally exposed to PCBs/PCDFs

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Abstract

Background: Polychlorinated biphenyls (PCBs) and related compounds such as polychlorinated dibenzofurans (PCDFs) and polychlorinated dibenzo-dioxins (PCDDs) alter sexual maturation and endocrine function in animals. In 1978–1979, a mass poisoning occurred in central Taiwan from cooking oil contaminated by heat-degraded PCBs and oxidated compounds PCDFs. We tested the hypothesis that in utero exposed to PCBs/PCDFs alter sexual maturation, endocrine, and reproductive function in the human pubescent females.

Methods: In 1997–1999, girls aged 13–19 years, born to mothers exposed to PCBs/PCDFs, was invited to participate in the study. Menstruation characteristic was recorded daily for 84 days and serum levels of estradiol, LH, FSH, and testosterone were measured on the 3rd day of menstruation.

Results: A total of 17 exposed girls and controls participated, the exposed girls reported shorter mean duration of bleeding per cycle than 16 unexposed (5.5 vs 6.5 days, $P = 0.0055$). There was a higher rate of irregular menstrual cycle in the exposed girls (40% vs 0%, $P = 0.018$). Serum levels of estradiol ($P = 0.016$) and FSH ($P = 0.061$) were higher in exposed girls as compared to controls.

Conclusions: We conclude that prenatal exposure to PCBs/PCDFs resulted in abnormal menstruation and higher estradiol and FSH levels in follicular phase of menstrual cycle in adolescent girls.

Abbreviations: PCBs, polychlorinated biphenyls; PCDDs, polychlorinated dibenzofurans (PCDFs) and polychlorinated dibenzo-dioxins; TCDD, tetrachlorodibenzo-*p*-dioxin; HAHs, halogenated aromatic hydrocarbons; LH, luteinizing hormone; FSH, follicle stimulating hormone; RIA, radioimmunoassay; E2, estradiol; TTR, transthyretin; NCKUMC, National Cheng Kung University Medical College.

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1. Introduction

There is a concern that environmental chemicals can alter endocrine functions in human beings. Polychlorinated biphenyls (PCBs) and related compounds such as polychlorinated dibenzofurans (PCDFs) and polychlorinated dibenzo-dioxins (PCDDs) are among the most widely spread environmental pollutants (Anderson, 1989). These compounds alter sexual maturation and endocrine function in animals (Theobald and Peterson, 1994; Brouwer et al., 1999; Hany et al., 1999). The most significant effects of halogenated aromatic hydrocarbons (HAHs) on the female reproductive system in rats and monkeys was decreased fertility, inability to maintain pregnancy for the full gestational period in monkeys, and decreased litter size in rats (Rier et al., 1993; Theobald and Peterson, 1994). PCBs and PCDDs were known to be ovotoxic. Reduced plasma concentrations of estrogen and progesterone, and signs of ovarian dysfunction such as anovulation and suppression of the estrous cycle have been reported (Kociba et al., 1976; Allen et al., 1979; Barsotti et al., 1979; Sager and Girard, 1994). In humans, girls with higher exposure to polybrominated biphenys in Michigan (PBB cohort) were found to have earlier age at menarche and earlier pubic hair development (Blanck et al., 2000). Among women exposed to TCDD in Seveso, Italy, pre-menarcheal exposure were associated with prolonged menstrual cycle. However, such effects were not observed in those exposed after menarche (Eskenazi et al., 2002).

In 1978–1979, a mass poisoning occurred in central Taiwan from cooking oil contaminated by heat-degraded PCBs and oxidated compounds PCDFs. The illness was referred to ''Yucheng'' (oil disease), and about 2061 people were included in a registry set up and maintained by the Taiwan Provincial Department of Health (Hsu et al., 1985). One hundred and eighteen Yucheng children born to Yucheng women between July 1978 and March 1985 and their matched non-exposed controls were identified in 1985 and have been followed since (Rogan et al., 1988). Tanner stage was assessed while the children went through puberty, and the preliminary results showed that Yucheng boys have lower Tanner stage than their controls at age 15, and they have shorter penis at ages 10–15 (Ryan et al., 1994; Guo et al., 1997). Yucheng girls had no apparent delays in sexual maturation. However, no study has been performed to examine the endocrine and reproductive function of these girls when they became sexually mature.

A similar PCBs/PCDFs poisoning incident involving 1862 persons occurred in Japan in 1968 (Tsukamoto et al., 1969). Irregular menstrual cycles were observed in 58% of 81 female victims in 1970, and urinary excretion of estrogens, pregnanediol, and pregnantriol tended to be low in these Yusho women (Tsukamoto et al., 1969).

The effects of PCBs/PCDFs and related compounds on sexual maturation, endocrine and reproductive functions in females have not been as well studied and characterized as those in males. The Yucheng children cohort provides a good opportunity to test the hypothesis that in utero exposure to PCBs/PCDFs alters sexual maturation, endocrine, and reproductive function in the human post-pubescent females. We tested the hypothesis that in utero exposed to PCBs/PCDFs alter sexual maturation, endocrine, and reproductive function in the human pubescent females.

2. Methods and materials

2.1. Study subjects

From 1979 to 1983, the Taiwan provincial Department of Health registered 2061 cases based on signs and symptoms of the illness or history of consumption of the contaminated oil. The Yucheng registry and health follow up are described elsewhere (Guo et al., 1999; Yu et al., 2000). In April 1985, 118 Yucheng children born to Yucheng mothers between July 1978 and March 1985 were identified by Rogan and Hsu (Rogan et al., 1988), and for each Yucheng child, a control child matched on age (within 15 days for those under one year in 1985, and within one month for those older), gender, area of residence, maternal age, and combined parents' educational level and occupational class was selected.

The follow-up study of the Yucheng adolescents was conducted in 1997–1999, approximately 20 years after the exposure accident. The Yucheng girls aged 13–19 years in 1997 and had reached Tanner stages four to five by July 1997. When a Yucheng adolescent agreed to participate, her control was recruited. Informed consent and parental permission were obtained from participating adolescents. The potential study subjects were in good health, not pregnant or lactating, and were not be so for at least one year. Thus the final sample included 48 girls.

2.2. Medical history and menstruation characteristic

All participants were first telephone interviewed for demographic characteristic, medical and pregnancy histories, and menstruation characteristic. The interviewers described the study as a health survey conducted by

National Cheng Kung University Medical College (NCKUMC), and did not mention Yucheng or PCBs specifically. The interviewers were not told the exposure status of the subject; and were not specifically aware of hypotheses concerning reproductive or menstrual dysfunction. The subjects were then instructed to record daily bleeding status and the number of pads used during menstruation on a diary for two consecutive menstrual cycles. All subjects were taught to use diary records for 84 days.

2.3. Serum hormones

Taiwan has local public health offices in every village, town, and city precinct. The local public health nurses were notified when the subject girls started menstruation, and they assisted in drawing blood samples for each subject in the early mornings (8 A m) of the third day of menstruation. The serum was immediately spun off using a portable centrifuge and frozen at −80 °C. Serum levels of estradiol, luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone were measured by radioimmunoassay (RIA) at NCKUMC laboratory by using commercial RIA kits (Diagnostic Products Corp., Los Angeles, CA).

2.4. Statistical analysis

Although the selection of controls was a matched procedure, some of the exposed subjects had no match among the successfully interviewed controls, and some of the exposed subjects for which there were interviewed controls were not successfully interviewed. Thus, when we compared frequencies or means, we used unpaired χ^2 and t tests. For comparisons between Yucheng and control girls of measurements not normally distributed, such as menstrual cycle length, non-parametric approach (Wilcoxon ranked sum test) was used. Furthermore, the data of serum hormonal levels which were log-normally distributed (estradiol, LH, FSH, testosterone) were log-transformed. Analyses were carried out using the JMP version 5.0 for the personal computer (SAS Company).

3. Results

Forty-eight young female adolescents, i.e., 27 Yucheng and 21 unexposed, participated in the study. Except for a tendency of increased common cold in the 12 months in Yucheng girls, there was no significant difference between Yucheng adolescents and the unexposed adolescents with regard to demographic characteristics and medial history (Table 1). The participating Yucheng and unexposed girls were similar in exercise frequency, tobacco and alcohol use.

The results of menstruation and reproductive function are shown in Table 2. Among the Yucheng and unexposed adolescents, none had ever being pregnant. None of the Yucheng and only one unexposed adolescent reported ever having intercourse. The average ages at menarche were similar between the two groups. The menstrual functions including duration of menstrual bleeding per cycle, menstrual cycle length, dysmenorrhea, ever missed menstruation in the past 6 months, ever visited a doctor due to menstruation problems (dysmenorrhea, irregular menses or abnormal amount of menses) were similar between the participating Yucheng and unexposed girls.

Daily records were completed in 17 Yucheng and 16 control girls (Table 3). Menstrual cycle length was not different between Yucheng and control girls. Yucheng girls reported shorter mean duration of bleeding per cycle than unexposed and the difference was significant (5.5 vs 6.5, $P = 0.0055$). Similar percent of Yucheng and control girls recorded mean cycle length of longer than or equal to 35 days. However, more Yucheng girls recorded mean cycle length of shorter than or equal to

Table 1
Characteristic and medical history of female Yucheng and unexposed adolescents

	Yucheng ($n = 27$)	Unexposed ($n = 21$)	P-value[a]
Age (year)	16.6 ± 0.5	17.2 ± 0.4	0.55
Height (cm)	154.8 ± 0.9	157.0 ± 1.1	0.13
Weight (kg)	49.3 ± 1.6	50.8 ± 1.3	0.52
Exercise per week (h)	3.3 ± 1.3	1.9 ± 0.4	0.40
# of Smokers (%)	2 (7.4%)	0 (0%)	0.20
Ever had asthma	1 (3.7%)	0 (0%)	0.37
Ever had skin allergy	8 (29.6%)	3 (14.3%)	0.21
Had common cold in the past 12 months	24 (88.9%)	14 (66.7%)	0.059
Mother PCBs levels in pregnancy (ppb whole serum)	47.5 ± 8.9	1.7 (pooled sample)	0.0001 (one-sample t-test)

In rows 1–4, 9, entries are mean SE. In rows 5–8, entries are number (%). None of the subjects admitted regular alcohol consumption. Ns: not statistically different.

[a] Independent t-test or Chi-square test.

Table 2
Menstruation and reproductive function of female Yucheng and unexposed adolescents

	Yucheng ($n = 27$)	Unexposed ($n = 21$)	P-value[a]
Ever being pregnant	0	0	1.0
Ever had intercourse	0	1 (4.8%)	0.25
Ever had masturbation	2 (7.4%)	5 (23.8%)	0.11
Age at menarche (year)	12.8 ± 0.3	12.7 ± 0.3	0.80
Duration of menstrual bleeding per cycle (days)	5.7 ± 0.2	6.0 ± 0.3	0.35
Menstrual cycle length (days)	30.4 ± 1.4	29.8 ± 0.2	0.66
Dysmenorrhea	1 (3.7%)	0	0.37
Ever without MC for 6 months	4 (14.8%)	7 (33.3%)	0.24
Doctor visit due to dysmenorrhea	2 (7.4%)	2 (9.5%)	0.79
Doctor visit due to irregular menses	4 (14.8%)	3 (14.3%)	0.96
Doctor visit due to abnormal amount of menses	1 (3.7%)	0	0.37

In rows 1–3 and 7–11, entries are number reporting the item (%).
In rows 4–6, entries are mean ± SE.
[a] t-test or Chi-square test.

Table 3
Menstruation characteristics by girls' daily records for 84 days

	Yucheng ($n = 17$)	Unexposed ($n = 16$)	P-value
Menstruation cycle length (days, median)	26.5	31.3	0.10[a]
Duration of bleeding per cycle (days, mean ± SE)	5.5 ± 0.2	6.4 ± 0.3	0.0055[b]
Cycle length of >34 days, number (%)	5 (29.4%)	7 (43.8%)	0.39[c]
Cycle length of <25 days, number (%)	6 (35.3%)	1 (6.3%)	0.032[c]
Dysmenorrhea, number (%)	10 (58.8%)	9 (57.6%)	0.88[c]
Medicated for dysmenorrhea, number (%)	2 (11.8%)	3 (18.7%)	0.58[c]

[a] Wilcoxon ranked sum test.
[b] t-test.
[c] Chi-square test.

25 days and the difference was significant (35.3% vs 6.3%, $P = 0.032$). Similar proportion of girls reported dysmenorrhea and taking medication for dysmenorrhea. Information on breast-feeding was obtained among 26 Yucheng girls. Due to pre-warning from the Department of Health after Yucheng episode, breast-feeding was discouraged and only 7/26 (26.9%) Yucheng daughters were breastfed, with a relatively short average duration of 5.8 weeks (SD = 12.4; range = 0–50 weeks) (Data not shown). The day of birth ranged from during the exposure to 5.2 years after the end of exposure around October 1979 (Data not shown). Duration of breast-feeding and day of birth after the end of exposure were not related to the reduced duration of menstrual bleeding.

A total of 38 girls (20 Yucheng and 18 controls) donated their blood during follicular phase (3 days after menstruation started) for serum hormonal analysis (Table 4). The serum hormonal data were log-normally distributed and thus log-transformed for analysis. Serum levels of estradiol ($P = 0.016$) were higher in the Yucheng subjects. There was also a tendency of elevated FSH in Yucheng girls as compared to unexposed. There were no significant differences in the serum levels of LH, and testosterone.

4. Discussion

Our results suggest that PCBs/PCDFs exposure in utero is associated with unchanged age at menarche, higher estradiol concentration at follicular phase, shortened menstrual cycle, and reduced bleeding time in girls in the early post-pubertal age. To the best of our knowledge, there are very few studies on reproductive functioning in girls with prenatal exposure to PCBs and PCDFs.

We found that age at menarche among Yucheng daughters was not different from their controls. This is similar to the study on Michigan angler cohort (Vasiliu et al., 2004), which found that daughter's age at menarche was not affected by maternal pregnancy serum level of PCBs at the range of 0–16.1 μg/l. However, maternal level of DDE during pregnancy lowered daughter's age

Table 4
Serum hormonal levels on the 3rd morning of menstruation period of Yucheng and unexposed girls

	Yucheng (n = 20)	Unexposed (n = 18)	P-value[a]
Estradiol (pg/ml)	39.4 ± 5.9	24.2 ± 3.5	0.016
LH (mIU/ml)	3.7 ± 0.4	4.8 ± 0.9	0.54
FSH (mIU/ml)	5.2 ± 0.4	4.3 ± 0.4	0.061
Testosterone (ng/dl)	0.3 ± 0.03	0.3 ± 0.03	0.87

Entries are mean ± SE.
The data were log-transformed.
[a] t-test.

at menarche. We did not find obvious difference of DDE levels between Yucheng and control mothers (Guo et al., 1997) and therefore could not examine the effects of DDE on menarche. In rats prenatally exposed to 2.5 ng/kg maternal weight or higher doses of 3,3′,4,4′,5-pentachlorobiphenyl, delayed vaginal opening as well as delayed start of regular cyclicity was observed (Muto et al., 2003), which is different from exposed humans.

The Yucheng girls were found to have shortened bleeding duration, as well as higher percentage of reported cycle length shorter than 26 days (Table 3) as compared to controls. In women directly exposed to TCDD in Seveso, prolonged cycle was found to be associated with serum levels of TCDD (Eskenazi et al., 2002). However, the persistent organic pollutants might exert different effects on females while exposed at different stages of development, i.e., directly exposed vs. exposed in utero. Thus different findings in menstrual characteristics between the directly exposed population and the second generation are not surprising. In rats, disturbed estrous cycle was observed only in the early stage after starting estrous cycle, with lengthened diestrous stage, in rats prenatally exposed to 2.5 ng/kg maternal weight or higher doses of 3,3′,4,4′,5-pentachlorobiphenyl, a coplanar PCBs (Muto et al., 2003).

Yucheng girls were found to have unchanged testosterone, higher estradiol and borderline elevation of FSH in follicular stage of the menstrual cycle as compared with controls. To our best knowledge, no report was published on human sex hormone effects during adolescence in prenatally exposed population. In weanling female rats (age = 21 days) prenatally exposed to 0, 0.5, 2, or 4 mg/day/kg maternal body weight of mixture of polychlorinated biphenyls, dose-dependent reductions of serum testosterone and estradiol (E2) concentrations were detected (Kaya et al., 2002). In rats with in utero and lactational exposure (maternal dose 2.5 μg/kg) to 2,3,7,8-TCDD, eCG-induced elevation of serum E2 levels were significantly lower on day 25 when compared with controls. Serum E2 levels were below assay sensitivity on Day 23 in both control and exposed animals (Salisbury and Marcinkiewicz, 2002). In female rats prenatally exposed to 2.5 ng/kg maternal weight or higher doses of 3,3′,4,4′,5-pentachlorobiphenyl, serum E2 and progesterone levels at age 50 days was reduced (Muto et al., 2003). Proposed mechanisms included reduced healthy follicles in the ovary, reduced response of follicles to gonadotropin, increased metabolism of E2 by aromatase. In Yucheng girls, the finding of elevated E2 is different from those from rats, possible mechanisms may include reduced end-organ and hypothalamic sensitivity to E2, resulting in elevated FSH and circulating E2.

The Yucheng mother used the contaminated cooking oil for as long as 9 months, they were estimated to have consumed about 1 g of PCBs and 3.8 mg of PCDFs during that period (Lan et al., 1981), resulting in median serum PCBs levels on the order of 10–20 times higher than background for PCBs and 10 000 times higher for the penta-CDF. Hence, our Yucheng girls will expose highest dose and the major chemical hazard health may be PCDFs.

In conclusion, our study shows that 27 female Yucheng adolescents, being exposed to PCBs/PCDFs in utero, have shortened bleeding duration, as well as higher percentage of reported cycle length shorter than 26 days as compared to controls and higher hormones levels, e.g. higher estradiol in follicular stage. It is necessary to conduct further studies to elucidate the problem of reproductive function Yucheng children.

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