

# CHILDHOOD HEALTH AND DEVELOPMENT IN RELATION TO PERSISTENT ORGANOCHLORINE COMPOUNDS

## THE ENDOCRINE AND REPRODUCTIVE FUNCTION OF THE FEMALE YUCHENG ADOLESCENTS EXPOSED TO PCBS/PCDFS IN UTERO

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### 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<sup>1</sup>. These compounds alter sexual maturation and endocrine function in animals<sup>2</sup>. When given to adult animals in sufficient dosage to cause overt toxicity, tetrachlorodibenzo-*p*-dioxin (TCDD)- like congeners can decrease plasma androgen concentrations, cause abnormal testicular morphology, decrease spermatogenesis, and reduce fertility in male animals<sup>2</sup>. 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<sup>2</sup>. In some studies, reduced plasma concentrations of estrogen and progesterone, and signs of ovarian dysfunction such as anovulation and suppression of the estrous cycle have been reported<sup>3-5</sup>.

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 as "Yucheng" (oil disease), and about 2061 people were included in a registry set up and maintained by the Taiwan Provincial Department of Health<sup>6</sup>. 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<sup>7</sup>. 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<sup>8</sup>. 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 PCB/PCDF poisoning incident involving 1862 persons occurred in Japan in 1968<sup>9</sup>. 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<sup>10</sup>. Thyroid function was investigated in 123 patients in 1984, and the serum triiodothyronine (T<sub>3</sub>), thyroxine (T<sub>4</sub>) levels were significantly higher than the normal controls, while thyroid stimulating hormone (TSH) levels were normal<sup>11</sup>. There was no correlation between PCB levels and levels of these thyroid hormones.

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The effects of PCB/PCDF and related compounds on sexual maturation, endocrine and reproductive function 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 postpubescent females.

## Methods and Materials

### Study subjects -

Female Yucheng adolescents of ages 13-19 and their age ( $\pm 1$  month), area of residence, maternal age ( $\pm 3$  years), socio-economic status-matched controls were invited to participate in the study in 1997-1999.

### Medical history and menstruation characteristic -

All participants were first telephone interviewed for demographic characteristic, medical and pregnancy history, and menstruation characteristic. The subjects were then instructed to measure and record basal body temperature before arising immediately upon awakening every day, and record daily bleeding status and the number of pads used during menstruation on a diary for two consecutive menstrual cycles. Time and frequency of ovulation were analyzed from the body temperature record and the diary by a senior obstetrician.

### Serum and urinary hormones -

Blood samples were drawn for each study subject in the early mornings of the third day of menstruation and the 7<sup>th</sup> day after ovulation, and first morning void urine samples were collected by the study subjects daily during the two menstrual cycles. Serum levels of estradiol, LH, TSH, T3, T4, FSH, and testosterone, and urinary levels of estrogen, estrogen metabolites, and progesterone metabolite pregnanediol glucuronide were measured.

## Results and Discussion

Forty-eight young female adolescents, 27 Yucheng and 21 unexposed, participated in the study. The average age of Yucheng adolescents was  $16.6 \pm 0.5$  years and was  $17.2 \pm 0.4$  years for unexposed adolescents. The Yucheng subjects were on average 2 cm shorter than the unexposed subjects (Table 1), but the difference was not significant. More Yucheng subjects reported having allergy (29.6% vs. 14.3%) and having had common cold within the 12 months prior to the interview (88.9% vs. 66.7%), the difference of the common cold frequency was borderline significant ( $p=0.06$ ).

Table 1. Demographic characteristic and medical history of female Yucheng and unexposed adolescents

	Yucheng (n=27)	Unexposed (n=21)	p-val*
Age(year)	16.6 $\pm$ 0.5	17.2 $\pm$ 0.4	Ns
Height(cm)	154.8 $\pm$ 0.9	157.0 $\pm$ 1.1	Ns
Weight(kg)	49.3 $\pm$ 1.6	50.8 $\pm$ 1.3	Ns
Smoking	2 (7.4%)	0	Ns
Alcohol use	0	0	Ns
Exercise per week (hour)	3.3 $\pm$ 1.3	1.9 $\pm$ 0.4	Ns
Asthma	1 (3.7%)	0	Ns
Allergy	8 (29.6%)	3 (14.3%)	Ns
Other disease	5 (18.5%)	4 (19.1%)	Ns
Common cold in the 12 months prior to interview	24 (88.9%)	14 (66.7%)	0.06

In rows 1-3 and 6, entries are mean  $\pm$  SE

In rows 4-5, 7-10, entries are number reporting the item (percent)

\*Independent t-test or Chi-square test

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Table 2 shows the menstruation and reproductive function of the Yucheng and unexposed subjects. None of the Yucheng subjects and only one unexposed adolescent had ever had intercourse. The average ages at menarche were similar between the two groups. In comparison with the unexposed adolescents, the Yucheng adolescents had smaller proportions of those who had ever masturbated (7.4% vs. 23.8%) and those who had no menses for more than six weeks within the 12 months prior to the interview (14.8% vs. 33.3%). The Yucheng adolescents had a larger proportion of those who had experienced menorrhagia (59.3% vs. 47.6%). However, none of the differences were statistically significant. For the two menstrual cycles observed, a higher percent of the Yucheng adolescents (40% vs. 22%) had observed ovulation, but the difference was not significant.

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

	Yucheng (n=27)	Unexposed (n=21)	p- val*
Ever being pregnant	0	0	Ns
Ever have intercourse	0	1 (4.8%)	Ns
Masturbation	2 (7.4%)	5 (23.8%)	Ns
Age at menarche (year)	12.8 ± 0.3	12.7 ± 0.3	Ns
Duration of menstruation (days)	5.7 ± 0.2	6.0 ± 0.3	Ns
Menstrual cycle (days)	29.3 ± 0.8	29.8 ± 0.2	Ns
Menorrhagia	16 (59.3%)	10 (47.6%)	Ns
Ever without MC for 6 months	4 (14.8%)	7 (33.3%)	Ns
Doctor visit due to menorrhagia	2 (7.4%)	2 (9.5%)	Ns
Doctor visit due to irregular menses	4 (14.8%)	3 (14.3%)	Ns
Doctor visit due to abnormal amount of menses	1 (3.7%)	0	Ns
<b>Ovulation</b>	<b>6 (40.0%)</b>	<b>4 (22.2%)</b>	<b>Ns</b>

In rows 1-3 and 7-12, entries are number reporting the item (percent)

In rows 4-6, entries are mean ± SE

\* Independent t-test or Chi-square test

Table 3. Serum hormonal levels of female Yucheng and unexposed adolescents

	Yucheng (n=20)	Unexposed (n=18)	p- val*
<b>Day 3 of Menses</b>			
Estradiol(pg/ml)	37.62 ± 4.25	26.43 ± 3.46	0.05
LH(mIU/ml)	3.87 ± 0.38	4.84 ± 0.89	ns
TSH(IU/ml)	1.68 ± 0.19	1.19 ± 0.13	0.04
T3(ng/dl)	108.01 ± 10.76	107.25 ± 4.16	ns
T4(ug/dl)	7.29 ± 0.35	6.73 ± 0.26	ns
FSH(mIU/ml)	5.19 ± 0.28	4.37 ± 0.34	0.07
Testosterone(ng/dl)	0.26 ± 0.04	0.27 ± 0.03	ns
<b>Seven Days After Ovulation</b>			
Estradiol(pg/ml)	96.92 ± 21.19	79.70 ± 12.87	ns
LH(mIU/ml)	10.16 ± 1.93	17.45 ± 9.00	ns
TSH(IU/ml)	1.76 ± 0.29	1.17 ± 0.14	0.07
T3(ng/dl)	100.58 ± 6.82	107.76 ± 5.79	ns
T4(ug/dl)	6.97 ± 0.43	6.87 ± 0.29	ns
FSH(mIU/ml)	5.18 ± 0.45	3.90 ± 0.56	ns
Testosterone(ng/dl)	0.29 ± 0.04	0.31 ± 0.03	ns

Entries are mean ± SE

\*Independent t-test or Chi-square test

### ORGANOHALOGEN COMPOUNDS

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Serum hormonal analysis for 38 study subjects showed that in both menstrual and ovulation stages, the Yucheng subjects had higher estradiol, TSH, and FSH levels, and lower LH levels than the unexposed adolescents (Table 3). Only the difference of the TSH level on the 3<sup>rd</sup> day of menses was statistically significant.

Our study result is not consistent with that of studies of the Yusho women. Irregular menstrual cycle, lower urinary excretion of estrogens, pregnanediol, and pregnantriol, and higher serum triiodothyronine (T3), thyroxine (T4) levels were found in the Yusho patients<sup>10,11</sup>. We did not find any abnormality in menstruation in the Yucheng adolescents, and they had higher serum estradiol level than their controls. This inconsistency could be due to the fact that the Japanese studies reported results from directly exposed Yusho women, and their time of examination was close to the Yusho incident; we studied female adolescents exposed to PCBs/PCDFs *in utero*, and the time lag between Yucheng incident and the examination was longer in our study. It is also possible that our sample size is small and the observation period, two menstrual cycles, is not long enough to observe regular pattern of the endocrine and reproductive functions.

Our study shows that 27 female Yucheng adolescents, being exposed to PCBs/PCDFs *in utero*, did not have abnormal menstruation, reproductive, or endocrine function when compared to the unexposed adolescents.

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