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MENSTRUATION AND REPRODUCTION IN WOMEN WITH PCB POISONING: LONG-TERM FOLLOW-UP INTERVIEWS OF THE WOMEN FROM THE TAIWAN YUCHENG COHORT

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Introduction

Mass poisonings in Japan in 1968¹ and in Taiwan in 1979,² each involving about 2000 persons, demonstrated that severe health consequences could arise from ingesting heat-degraded polychlorinated biphenyls (PCBs). In both events, PCBs used as heat exchangers contaminated rice bran cooking oil during processing. These PCBs had been thermally degraded and were thus contaminated by polychlorinated dibenzofurans (PCDFs) and polychlorinated terphenyls and quaterphenyls³. The clinical syndrome occurring with a history of having consumed the contaminated oil was called Yusho or Yucheng, "oil disease" in Japanese and Chinese respectively.^{1,2} Thirteen years later, an investigation of levels of the compounds among 56 Yucheng women showed that they still had mean levels of total PCBs 7.3 times those found in Taiwanese people with only background exposure (2820 parts per billion in fat of serum vs 386 ppb), 40 times background for the 2,3,4,7,8 penta CDF (1090 parts per trillion vs 28 ppt), and 128 times background for the 1,2,3,4,7,8 hexa CDF (2560 ppt vs 20 ppt)⁴. The whole cohort has excess mortality from non-malignant liver disease after 13 years of follow-up.⁵ Following the study on mortality, we did a morbidity survey confined to surviving members of the cohort and controls who were 30 years and older in 1993.

Materials and methods

From 1979 to 1983, the Taiwan Provincial Department of Health registered 2061 cases based on signs and symptoms of the illness or a history of consumption of the contaminated oil.² We acquired the registry from the Department of Health in 1991. Using the address listed in the Yucheng registry, we traced them through December 31, 1991. Among the 2061 subjects included in the Yucheng registry, 70 were actually offspring of the exposed subjects who were born during or after the incident, and so were excluded. 1837 subjects were located through their neighborhood household registration offices' records. 986 (54%) persons in the cohort who were located were female, of whom 36 had died by December 31, 1991.⁵ The overall morbidity survey⁶ of which the women's reproductive study was a part was limited to those 30 years of age and older in 1993, in whom the majority of health impairment was expected to occur. In addition, the women's reproductive study was limited to women who were 59 or younger in 1993, and thus 45 or younger when the exposure occurred in 1979 and therefore likely to have been pre-menopausal then. There were 600 such women alive on December 31, 1991. We attempted to find and interview all of them.

We used the 1979 addresses of the registry members as index addresses and attempted to identify the persons who lived nearby in 1979 from the archives of the registration offices. We identified three controls for each registry member, and we attempted to contact the control subject living nearest to the index address in 1979. We found 594 control women in the eligible age range. The interviews took place between July 1993 and June, 1994. The interviewers described the

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study as a health survey conducted by Cheng Kung University Medical College, and did not mention Yucheng or PCBs specifically. The interviewers were not told the exposure status of the subject; however, some women volunteered that they had been Yucheng victims.

We were able to contact 368 of the remaining women. Twelve of the exposed women and seventeen of the controls refused to be interviewed, and so we had usable interviews from 356 exposed and 312 controls.

Results

Demographic characteristics of the women are in Table 1. Overall, the percentage reporting abnormalities of menstrual flow was 16.6% vs 7.5% ($p < 0.05$) (Table 2). The percentage reporting irregular cycles, dysmenorrhea, the reported frequency of sexual intercourse, the percentage who had experienced menopause and the mean age at menopause were similar in the Yucheng women and the controls. Among the Yucheng women, 342 (of the 356) had ever married, and among the controls 302 (of 312) had ever married. Only four of these Yucheng women and three controls had no living children. The average number of living children was the same in both groups, 3.1 (Table 3). The Yucheng women reported stillbirths since 1979 2.5 times more frequently than the controls ($p = 0.068$), but spontaneous abortion frequency was similar in both groups. Among the Yucheng women, 33 (10%) reported 35 deaths among their offspring during childhood, and 18 (6%) control women reported 18 deaths. Among the deaths reported by the Yucheng women, eight had no dates reported, nine (33%) occurred before 1979 (unexposed children), three (11%) occurred during or after 1979 to children born before 1979 (directly exposed children), and 15 (55%) occurred in children born during or after 1979 (transplacentally exposed children). Among the deaths reported by the control women, four had no dates recorded, five (36%) occurred before 1979, three (21%) occurred during or after 1979 in children born before 1979, and six (43%) occurred in children born during or after 1979. The numbers of women who reported needing longer than a year to get pregnant or getting treated for infertility were small. A higher percentage of Yucheng women had decided to limit childbearing because of health problems (7% vs 2%, $p < 0.05$), most frequently their PCB poisoning (Table 3).

Discussion

In this retrospective survey, about twice as many Yucheng women as controls reported having abnormal menstrual flow; they did not, however, report more irregular or painful cycles, different age at menopause, or differences in frequency of sexual intercourse. They were not asked about more specific conditions such as endometriosis or fibroids. More of the Yucheng women had decided to limit childbearing because of health problems. However, Yucheng women who did not choose to limit their family size had the same number of children as controls, arguing against a severe impairment of their fertility. Although more of the Yucheng children were stillborn or died during childhood, the mean number of living children among Yucheng and control families was the same. Our findings suggest that Yucheng women exposed to high dose of PCBs/PCDFs have relatively mild interference with menstrual function, and no change in fertility as measured by family size or requiring infertility treatment, or libido as measured by frequency of intercourse. They do report more frequent stillbirths and higher mortality among their children, and from other studies it is known that their surviving children have excess ectodermal defects, developmental delay, and disordered behavior.⁷ These women had exposures high enough to make them clinically ill. Their experience should represent the upper bound of expected toxicity from background exposures. Given the extensive experimental literature on the reproductive toxicity of the PCBs and similar compounds, we think it very likely that there is menstrual dysfunction in these women, and that further study to determine the extent of dysfunction and its mechanism, especially among the younger women, is warranted.

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Acknowledgements:

Supported by grants from the National Science Council of Taiwan, NSC 81-0421-B-006-06YZ and NSC 83-0421-B-006-064YZ. Dr. Rogan was the recipient of a three-month NSC Visiting Scientist grant at National Cheng Kung University during some of the writing of this paper.

Table 1 Demographic characteristics of the Yucheng and control women, 1993-4

Characteristic	% of <u>Yucheng</u> women (N=356)	% of Control women (N=312)
Age group (years)		
30-39	51.1	51.6
40-49	32.0	30.1
50-59	16.9	18.3
Marital status	%	%
Single	3.9	3.2
Married	91.6	93.6
Divorced or widowed	4.5	3.2
Education years		(n=311)
	%	%
0-6	63.6	66.1
7-12	30.7	29.7
13-16	5.7	4.2
Smokers		(n=311)
	%	%
	0.8	0.6
Alcohol consumption	(n=355)	(n=311)
	%	%
None	89.9	90.0
< one drink/week	9.0	8.0
≥ one drink/week	1.1	1.9

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Table 2 Menstruation and frequency of intercourse among Yucheng and control women, by exposed/control status, 1993-4

Variable	All <u>Yucheng</u> women (N=356)	Control women (N=312)
Irregular menstrual cycle	58/335, 17.3%	45/292, 15.4%
Abnormal menstrual flow	55/331, 16.6%	22/293, 7.5%*
Dysmenorrhea	34/319, 10.7%	26/280, 9.3%
Intercourse (per month)	(n=279) 3.6 ± 0.18	(n=238) 3.6 ± 0.18
Experienced menopause	75/347, 21.6%	68/306, 22.2%
Mean age at menopause	(n=60) 47.3 ± 0.76	(n=58) 46.7 ± 0.94
Cause of menopause	(n=61)	(n=66)
Natural	51	52
Surgical	9	13
Other	1	1

p<0.05

Table 3 Reproductive outcome among ever-married Yucheng and control women, by exposed/control status, 1993-4

Variable	All <u>Yucheng</u> women (N=342)	Control women (N=302)
Mean number of living children	3.1 ± 0.1, n=340	3.1 ± 0.1, n=298
Spontaneous abortion since 1979	23/336, 6.8%	22/297, 7.4%
Stillborn infant since 1979	14/336, 4.2%	5/297, 1.7%*
Ever had a child die before adolescence (see text for dates)	33/331, 10.0%	18/294, 6.1%**
Ever took longer than one year to become pregnant	9/332, 2.7%	9/296, 3.0%
Ever had a diagnosed fertility problem	5/332, 1.5%	6/295, 2.0%
Ever decided to limit childbearing for health reason	23/335, 6.9%	6/295, 2.0%**
Reason	(n=15)	(n=3)
Reproductive system	1	3
Other system	3	0
PCB poisoning	11	0

*p=0.068, all Yucheng women vs control; **p<0.05, all Yucheng women vs control