

Follow-up Study of Reproductive Hazards of Multiparous Women Consuming PCBs-Contaminated Rice Oil in Taiwan

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In 1979, an epidemic of a peculiar skin disease occurred in central Taiwan. About 2000 persons had common symptoms of acne-form eruptions, follicular accentuation, pigmentation of skin and nails as well as hypersecretion of meibomian gland. Investigations showed that affected individuals had consumed rice oil contaminated with polychlorinated biphenyls (PCB) and thermal degradation products of PCB, including polychlorinated dibenzofuran (PCDF) and polychlorinated quarterphenyls (PCQ) (Chen et al. 1981; Hsu et al. 1985). Similar chemical exposure and clinical findings occurred in Japan, 1968. Rice-oil disease was called 'Yusho' in Japanese and 'Yu-Cheng' in Chinese (Hsu et al. 1985).

PCB is lipophilic aromatic hydrocarbons. In Japanese studies of Yusho poisoning, PCB and PCDF were transferred through poisoned mothers to their fetuses via placenta and breast milk (Yoshimura 1974), causing stillbirth and undersized infants (Taki et al. 1969; Yamaguchi et al. 1971). The offspring of poisoned women may be susceptible to the potential health hazards of PCB intoxication. These babies born to poisoned mothers were called 'PCB transplacental Yusho babies' in Japan (Yoshimura 1974), and 'PCB transplacental Yu-Cheng babies' in Taiwan (Lan et al. 1987a).

In Taiwan, major victims of PCB poisoning were students and factory workers 11 to 30 years of age (Hsu et al. 1985). About 800 poisoned women of reproductive age might have been married or would get married after the poisoning. According to the age-specific general fertility rate in Taiwan, it was estimated about 270 PCB transplacental Yu-Cheng babies were born to these women between 1979 and 1986 (Department of Health 1986). Therefore, reproductive hazard was the most important problem under this circumstance. Only two previous studies in Taiwan described including the PCB fetal syndrome, abnormal liver function and widening of anterior fontanelle of transplacental Yu-Cheng babies (Wang et al. 1981; Law et al. 1981). The study of Hsu et al. (1985) reported a high infant mortality of transplacental Yu-

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Cheng babies (8/39=20.5%). Our previous studies showed a significant difference in the clinical features between PCB-poisoned mothers and their transplacental Yu-Cheng babies (Lan et al. 1987a), and reported the clinical symptoms and physical examination findings of one transplacental Yu-Cheng baby from birth to death in 23.5 months in detail (Lan et al. 1987b). Up to now, the number of reported cases were too small for following up reproductive outcomes (Rogan et al. 1985).

The complete reproductive outcomes of PCB-poisoned women were assessed in this study. The results include birth weights, placental weights, prenatal conditions, infant weights and growth curves of babies affected by transplacental PCB intoxication.

MATERIALS AND METHODS

Data was collected by personal interview and from medical records of a teaching hospital in central Taiwan, where the PCB poisoning occurred. Only five multiparous PCB poisoned women with complete delivery history after PCB poisoning were included in this study. The history of pregnancy and delivery of these five women were recorded in detail. The growth of their Yu-Cheng babies were carefully measured by pediatricians of the teaching hospital. Information on age, parity and pregnancy outcomes of mothers after PCB poisoning, as well as sex, gestation age, birth dates, birth weights, placental weights, feeding history, 1 minute and 5 minutes apgar scores of transplacental Yu-Cheng babies were collected. Apgar score respectively indicated a summary results of an initial physical examination of neonates at 1 and 5 minutes after birth. The highest score obtainable is 10 and scores from 7 to 10 indicate a good prognosis for the baby regarding mortality and subsequent neurologic sequelae (Johnes et al. 1984).

The norm of placental weight by gestational age in Taiwan (Chen 1969) was used as a standard, while, the birth weight and apgar score of control population was derived from the birth records of the same teaching hospital. We collected birth data of 18828 male babies and 16926 female babies from 1977 to 1987 except 1980, and those of multiple pregnancies, stillbirth, and malformations (i.e. severe hydrocephalus or anencephalus) were excluded. In order to adjust sex and gestational week, summary Z test (Hogg and Craig 1978) was utilized to test the statistical significance of the difference in the birth placental weight, birth weight and apgar score between Yu-Cheng babies and its control population. In the statistical analysis, every measurement of each Yu-Cheng baby was first normalized based on the mean and standard deviation (SD) of control population with same sex and/or gestation week ($Z_i = (X_i - \text{Mean}) / \text{SD}$). Z_i scores were then summarized and divided the square root of case number ($Z = \sum Z_i / \sqrt{n}$) to derive the Z value.

Growth of seven transplacental Yu-Cheng babies were followed up in the baby health clinic. The growth curve of the body weight of children under the age of 6 years in Taiwan (Taiwan Provincial

Maternal and Child Health Institute 1982) was used as a standard to detect any growth retardation of these transplacental Yu-Cheng babies.

RESULTS AND DISCUSSION

These five multiparous women were PCB-poisoned with a high PCB level in blood (Ko et al. 1981)(Table 1). They were non-smokers, and all of them except M2 had normal delivery before the poisoning. After the poisoning, the total number of pregnancies of these five mothers was 17. Of these pregnancies, four fetuses aborted spontaneously (4/17=23.5%), one was stillbirth (1/17=5.9%), ten babies survived more than six months (10/17=55.8%), and two died before six months of age (2/17=11.8%). Among five first gestations after poisoning of each mother, three were aborted, one was small for date and died soon after birth, and only one survived (1/5=20%).

From the prospective study of Wu (1980), the spontaneous abortion and stillbirth rate of married women were about 57 per 1000 pregnancy in Taiwan from 1974 to 1975. The rate in our study subjects was about five-fold higher than married women in general population (294/1000 vs 57/1000). These results were consistent with observations of a positive association between the high PCB serum levels and the occurrence of missed abortion reported previously (Bercovici et al. 1983). Similarly, infant mortality rate in our study subjects was also significantly higher than that of the general population (16.7/1000 vs 6.8/1000, Department of Health 1986).

As for the intrauterine growth of transplacental Yu-Cheng babies, the birth weights of 6 babies in 12 live births were less than 2500 g (6/12=50%). Adjusting for gestational week and sex, there was a significant difference in birth weight of the control population ($Z=-2.96$, $P<0.01$). These results were the same as those reported in previous studies (Yamaguchi et al. 1971; Taki et al. 1969). But there was no difference in 1 minute and 5 minutes apgar scores between Yu-Cheng babies and control population ($Z=-0.54$ and $Z=-1.47$, respectively).

The low viability and intrauterine growth retardation of fetuses is most likely caused by the absorption of PCB through the placenta. As the birth weight correlates with the placental weight (Chen 1969), the reduction in size and weight of placenta was suspected to be the reason for PCB-poisoned women having high susceptible to spontaneous abortion. However, We found the placental weight of transplacental Yu-Cheng babies (Fig 1) was not significantly different from that of the control population ($Z=0.35$, $p>0.05$) (Chen 1969).

This result coincided with the study of Hedmen et al.(1985). They reported that PCB might cause a deterioration in the placental function of guinea pig by reducing its blood flow. There was no difference in placental weight of hexachlorobiphenyls-poisoned

Table 1. Birth records of PCB-poisoned multiparous mothers and their transplacental Yu-Cheng babies

PCB-poisoned mothers			Transplacental Yu-Cheng babies							
Birth year & No.	PCB in blood (1981)	Gravida after Poisoned	Birth date	Sex	Gesta-tional week	Birth weight (gm)	Placental weight (gm)	Apgar score at birth	Period of breast feeding	Health status
M1 1953	47	1	? 1979	?	25	-	-	-	-	Spontaneous abortion
		2	May 1980	?	?	-	-	-	-	Spontaneous abortion
		3 #	July 1981	F	42	2720	600	(7,8)	None	Live birth
		4 #	May 1983	F	44	3000	580	(8,9)	None	Live birth
		5 #	Jan. 1985	M	38	2940	500	(8,9)	None	Live birth
M2 1949	31	1	? 1979	?	10	-	-	-	-	Spontaneous abortion
		2 #	Oct. 1981	F	39	2000	460	(8,9)	None	Live birth
		3	Mar. 1983	F	20	400	400	-	-	Still birth
		4	May 1985	M	33	1900	485	(3,5)	None	Live birth
M3 1949	201	1	? 1979	?	10	-	-	-	-	Spontaneous abortion
		2 #	Sept. 1980	M	33	1620	500	(7,8)	None	Live birth
		3	Nov. 1982	?	27	850	300	-	-	Expired next day of delivery
M4 1954	688	1	July 1979	F	36	2020	400	(5,7)	3 months	Died from congenital heart disease(?) at 3 month
		2	Jan. 1981	M	35	2200	500	(7,9)	24 days	Live birth
		3 #	May 1982	M	38	2900	600	(8,9)	None	Live birth
M5 1955	12	1	Nov. 1980	M	38	3100	760	(8,9)	7 months	Live birth
		2 #	Dec. 1984	M	40	3440	600	(8,9)	None	Live birth

+ : average PCB concentration in blood (ppb) tested by Ko YC et al.(1981).

: growth analysis were done for these 4 boys and 3 girls.

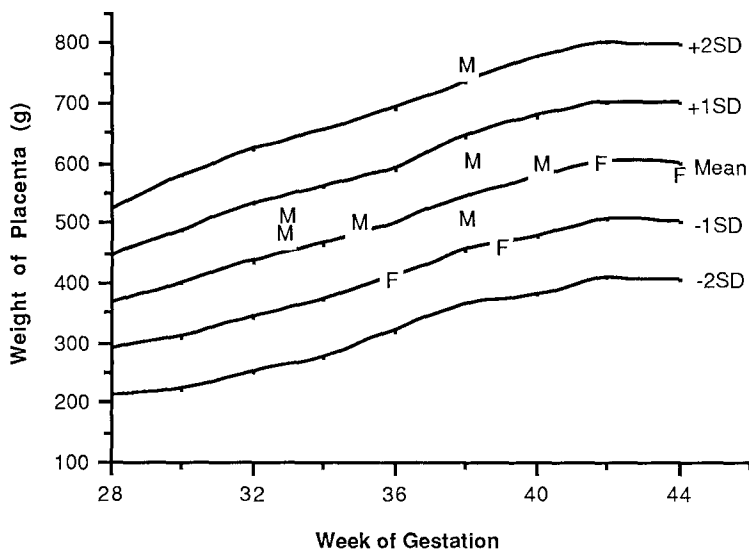


Figure 1. Scattergram of placental weight of Yu-Cheng babies. (M: male; F: female, and standard from Chen YP 1969). Two subjects were not plotted for absence of standard placental weight for the gestational week of less than 28.

animals compared with the referent group. It was thus reasonable to attribute the high abortion and infant death rates of these transplacental Yu-Cheng babies to the deterioration in the placental function through the reduction in blood flow rather than the reduction placental weight.

Only 3 transplacental Yu-Cheng babies were fed on PCB contaminated breast-milk. The female baby delivered by M4 in 1979 died from congenital heart disease after 3 month breast-feeding (Table 1). The quantity of PCB transferred to infants via lactation was much greater than that transferred through placenta, and the PCB level in blood of breast-fed infants rose markedly after the ingestion of contaminated human milk and tended to increase until 1 yr of age (Kodama and Ota 1980). Therefore, the high PCB level of breast milk might accelerate the death of Yu-Cheng baby.

From Table 1, it seemed that the most harmful effect always occurred in the first pregnancy after poisoning. But the hazard might still last for many gravidities. In previous studied in Japanese or Taiwanese, only the first birth after PCB poisoning was examined. There is a lack of detailed reproductive hazards followed up for many years. In the experimental study of non-human primates, rhesus monkeys ingesting a PCB mixture (Aroclor 1248) for a long period of time, were found to develop chloracne, menstrual irregularities, reduced conception rates, and increased incidence of abortion and small for date infant (Barsotti et al. 1976). Allen et al. (1980) reported that adult female monkeys having experienced severe PCB intoxication had a dramatic impro-

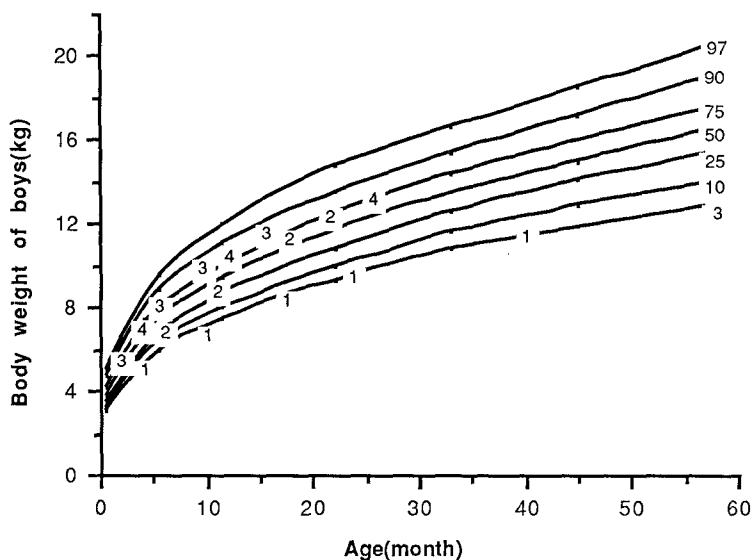


Figure 2. Growth patterns of body weights of 4 Yu-Cheng boys.
(standard from Taiwan Provincial Maternal and Child
Health Institute, 1982)

No. marked for Yu-Cheng boys	No. of poisoned mothers(Table 1)	Birth date of Yu-Cheng boys	Gravida after poisoned
1	M3	Sept.1980	2
2	M4	May 1982	3
3	M5	Dec. 1984	3
4	M1	Jan. 1985	5

vement in physical status within 1 yr after the PCB was eliminated from their diets. However, the offspring of these adult female monkeys were small at birth and developed signs of PCB intoxication similar to their siblings born while their mothers were ingesting PCB. These results suggested that the offspring of PCB-poisoned women would still suffer from PCB toxicity for a long period of time after the termination exposure to ingestion of PCB-contaminated oil.

As Yu-Cheng babies had intrauterine retardation, we further examined whether there was a growth retardation in infancy and childhood. As shown in Fig 2, body weights of these Yu-Cheng boys were within the normal range of the standard curves. There was one baby remained at the 3rd percentile in birth weight through the age up to 3.5 years. The reasons for this under growth might be due to premature birth, low birth weight and earlier birth order after poisoning.

From the Table 1, it is obvious that the birth weight of tran-

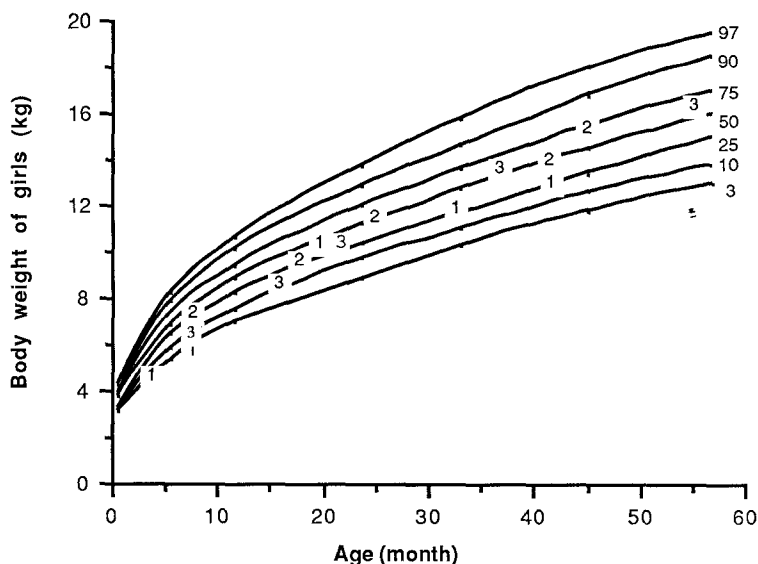


Figure 3. Growth patterns of body weights of 3 Yu-Cheng girls.
(standard from Taiwan Provincial Maternal and Child
Health Institute, 1982)

No. marked for Yu-Cheng girls	No. of poisoned mothers(Table 1)	Birth date of Yu-Cheng girls	Gravida after poisoned
1	M1	July 1981	3
2	M2	Oct. 1981	2
3	M1	May 1983	4

splacental Yu-Cheng girls was lower than that of the control population. But their growth in body weight showed a catch-up phenomenon (Fig.3) as male babies. There were two follow-up studies on the body-weight gain. One study (Yamaguchi et al. 1971) showed that the postnatal growth curve of Yusho babies were almost regression to the standard at the 9th months. The other (Hayashi et al. 1983) showed that growth curves of Yusho babies were always within 2 standard deviation of the standard from 2 to 15 years of age. Our results also demonstrated a catch-up of the growth of Yu-Cheng babies to normal in their early childhood.

It seems that more poisoned-women should be studied to validate effect of PCB on the spontaneous abortion, stillbirth and to examine the catch-up phenomenon of growth of their Yu-Cheng babies. While PCB-contaminated rice oil had been ingested, PCB and PCDF were retained in human body for a long period of time. Nevertheless, the time lag required for the fetus of these of PCB-poisoned women being free from PCB intoxication deserves further investigation.

REFERENCES

- Allen JR, Barsotti DA, Carstens LA (1980) Residual effects of polychlorinated biphenyls on adult nonhuman primates and their offspring. *J Toxicol Environ Health* 6:55-66
- Barsotti DA, Marlar RJ, Allen JR (1976) Reproductive dysfunction in rhesus monkeys exposed to low levels of polychlorinated biphenyls (Aroclor 1248). *Food Cosmet Toxicol* 14:99-103
- Bercovici B, Wassermann M, Cucos S, Ron M, Wassermann D, Pines A (1983) Serum levels of polychlorinated biphenyls and some organochlorine insecticides in women with recent and former missed abortions. *Environ Res* 30:169-174
- Chen YP (1969) Patterns of fetal and placental growth with intra-uterine growth chart in Chinese. *Obs Gyn China* 8:1-18
- Chen PH, Chang KT, Lu YD (1981) Polychlorinated biphenyls and polychlorinated dibenzofuran in toxic rice-bran oil that caused PCB poisoning in Taichung. *Bull Environ Contam Toxicol* 26:489-495
- Hayashi M, Yamashita F (1983) The growth and sexual maturation of patients with PCB poisoning. *Fukuoka Acta Med* 74:280-283
- Hedman C, Bjellin L, Martensson L (1985) The influence of 2,2', 4,4',5,5'-Hexachlorobiphenyl on the placental blood flow in guinea pigs at late stage of gestation. *Environ Res* 38:293-300
- Department of Health, Executive Yuan (1986) Health statistics : 2. Vital statistics 1986, Republic of China, Department of Health Taipei.
- Hogg RV, Craig AT (1978) Distribution of functions of random variables. In : Introduction to mathematical statistics, 4th ed. Macmillan, New York, p176
- Hsu ST, Ma CI, Hsu Steve KH, Wu SS, Hsu Nora HM, Yeh CC, Wu SB (1985) Discovery and epidemiology of PCB poisoning in Taiwan : A four-year follow up. *Environ Health Perspect* 59:5-10
- Johnes DA, Lepley MK, Baker BA (1984) Health assessment across the life span. McGraw-Hill Co., New York, 1st ed. p402-403
- Ko YC, Jao LT, Cheng CT, Hsu ST, Hsiao HC, Hu HT (1981) The blood level of PCB in the poisoned patients. *J Formosan Med Assoc* 80 :774-779
- Kodama H, Ota H (1980) Transfer of polychlorinated biphenyls to infants from their mothers. *Arch Environ Health* 35:95-100
- Lan SJ, Yang CY, Yang CH, Yen YY (1987a) A survey of clinical features of polychlorinated biphenyls poisoned mothers and their transplacental Yu-Cheng babies. *Kaohsiung J Med Sci* 3: 372-376
- Lan SJ, Tang SY, Ko YC (1987b) The effect of PCB poisoning : A survey of a transplacental Yu-Cheng babies : Report of a case. *Kaohsiung J Med Sci* 3:64-68
- Law KL, Hwang BT, Shaio IS (1981) PCB poisoning in newborn twin. *Clin Med(Taipei)* 7:88-91
- Rogan WJ, Gladen BC, Wilcox AJ (1985) Potential reproductive and postnatal morbidity from exposure to polychlorinated biphenyls :epidemiologic considerations. *Environ Health Perspect* 60:233-239
- Taiwan Provincial Maternal and Child Health Institute (1982) Growth charts of height, weight , and chest and head circumference for children under six years of age in Taiwan. Taiwan Provincial Maternal and Children Health Institute, Taichung.

- Taki I, Hisanaga S, Amagase Y (1969) Report on Yusho (chlorobiphenyls poisoning) pregnant women and their fetuses. Fukuoka Acta Med 60:471-474
- Wong KC, Hwang MY (1981) Children born to PCB poisoning mother. Clin Med (Taipei) 7:83-87
- Wu SC (1980) A prospective study on the abortion and stillbirth in Taiwan 1974-1975. J Demography of National Taiwan University 4:127-140
- Yamaguchi A, Yoshimura T, Kuratsune M (1971) A survey on pregnant women having consumed rice oil contaminated with chlorobiphenyls and their babies. Fukuoka Acta Med 62:117-122
- Yoshimura T (1974) Epidemiological study on Yusho babies born to mothers who had consumed oil contaminated by PCB. Fukuoka Acta Med 65:74-80

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