

## **Follow-up Study of Intrauterine Growth of Transplacental Yu-Cheng Babies in Taiwan**

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There was an outbreak in central Taiwan in 1979 of human PCB (polychlorinated biphenyls) poisoning caused by consumption of contaminated rice-bran oil (Hsu et al. 1985). The contamination involved PCDFs (polychlorinated dibenzofurans) and PCQs (polychlorinated quarterphenyls); both are thermal-degraded products of PCBs (Chen et al. 1985). The common symptoms of PCBs intoxication are acne-form eruption, follicular accentuation, pigmentation of skin and nails, as well as hypersecretion of the meibomian gland (Hsu et al. 1985). This disease is called 'Yusho' in Japanese (Yoshimura 1974) and 'Yu-Cheng' in Chinese (Hsu et al. 1985); both are translated as "oil-syndrome" literally. The PCBs, PCQs and PCDFs accumulate in adipose tissue, resist excretion, and are capable of transferring through poisoned women to their offspring via the placenta and/or breast milk to cause abnormalities (Yoshimura 1974; Masuda et al. 1978; Komada and Ota 1980).

There were a total of 1,978 Yu-Cheng patients registered by the government health agency. Most of them were females (1,046) and 68% of these females were in the age, range 10 to 39 years. These poisoned women were of reproductive or pre-reproductive age, and pregnancies after poisoning were likely. According to the age-specific general fertility rate in Taiwan, it was estimated that about 500 Yu-Cheng babies would be born to these women between 1979 and 1986 (Department of Health, Executive Yuan 1987) due to transplacental transfer of PCBs. The potential reproductive hazard, therefore, is a major concern.

In 1968, a similar PCB poisoning event with contaminated rice oil occurred in Japan (Kuratsune et al. 1969). Japanese studies reported that PCBs were transferred from poisoned mothers to their fetuses via the placenta,

causing intrauterine growth retardation, which led to small-for-date or stillbirth, pigmented skin, and widening of anterior fontanelle of the new-born (Fetal PCBs Syndrome) (Yamaguchi et al. 1971; Funatsu et al. 1971). Two studies have demonstrated that the symptoms of Yusho babies decreased with increasing gravidity (Yoshimura 1974; Lan 1982). Because of the very short period of follow-up and the small number of cases collected, there was no study on the time duration required for the fetuses of these PCB-poisoned women to be free from the effect of PCBs.

Low birth-weight, the most common feature of the Fetal PCBs Syndrome, might be due to intrauterine growth retardation or prematurity. This condition is associated with high infant mortality, congenital abnormality and developmental retardation (Susser et al. 1972; Harvey et al. 1982; Escalona 1982). We have collected data on birth weights and gestational weeks of transplacental Yu-Cheng babies to examine whether the elapsed time since maternal PCB ingestion or the increasing gravidity after poisoning diminish the retardation of intrauterine growth.

#### **MATERIALS AND METHODS**

This study included 78 PCB-poisoned women who had been pregnant or had given birth, after poisoning, between 1979 and 1986. The subjects were identified from family planning data at a local health center in the PCB-poisoning cluster area. Among a total of 184 pregnancies in the study group, there were 21 abortions or stillbirths, leaving 163 singleton births for analysis. The reproductive histories of these women were collected via interviewing, and the birth data of the transplacental Yu-Cheng babies were collected from medical records of the hospitals where the deliveries took place and were supplemented by the birth certificates in the local household registration offices. The study variables included maternal age and gravidity after poisoning, and the gender, birth date, length of gestation and birth weights of Yu-Cheng babies. The same data for 17 babies born by those mothers before poisoning episode were also collected.

The birth weight and gestational age of non-Yu-Cheng comparison babies were derived from the birth records of a teaching hospital in central Taiwan, the area where PCBs poisoning occurred. We collected live birth data for 18,865 male and 17,054 female singleton babies born between 1977 and 1987 (excluding 1980, which had incomplete birth records). Multiple pregnancies, stillbirth and malformations (i.e. severe hydrocephalus or anencephalus) were excluded.

Summary Z score (Hogg and Craig 1978) was used to adjust for the differences in sex and gestational age in comparison of birth weight of transplacental Yu-Cheng babies with that of the control population. In a previous study (Yen et al. 1990), we have reported that the distributions of birth weights and gestational ages all had high kurtosis and skewed to the left and that, conditional on gestational week, the distribution of birth weights can be normalized. Therefore in the analysis, the birth weight of each Yu-Cheng baby was first normalized based on the mean and standard deviation of birth weight of the control population with the same sex and gestational age to obtain an individual Z score;  $Z_i = (X_i - \mu_i) / \sigma_i$ , where  $X_i$  is the birth weight for Yu-Cheng baby  $i$ ,  $\mu_i$  and  $\sigma_i$  are mean and standard deviation from the control population of the same sex and gestational age. The scores were then summed and divided by the square root of the number of babies to derive the summary Z value ( $Z = \sum Z_i / \sqrt{n}$ ). Summary Z value tests whether birth weights of Yu-Cheng Babies were different from those of the control population (Hogg and Craig 1978).

## RESULTS AND DISCUSSION

One hundred sixty three 163 singleton live births were born to 78 PCB-poisoned women between 1979 and 1986, including 86 boys and 77 girls. The average age of these poisoned mothers at the time of the babies' births was  $25.6 \pm 3.4$  years old, the average gravidity was  $2.5 \pm 3.4$  overall and  $1.9 \pm 1.0$  after poisoning. The complete birth record was available for 130 live births (66 males and 64 females). There were no significant difference between Yu-Cheng babies and control population ( $25.6 \pm 3.4$  vs  $27.6 \pm 3.7$  years old,  $p > 0.05$ , for average of mothers' age;  $2.5 \pm 3.4$  vs  $2.2 \pm 1.3$ ,  $p > 0.05$ , for average of total gravidity). The rates of low birth weight and prematurity among Yu-Cheng babies, shown in Table 1, were significantly higher than those of the control population ( $27.7\%$  vs  $6.3\%$ ,  $p < 0.01$ , for low birth weight ;  $24.6\%$  vs  $8.1\%$ ,  $p < 0.01$ , for prematurity). The rate of prematurity among male Yu-Cheng babies was higher than that among females.

Table 2 shows that for the 17 babies born before the poisoning episode, adjusting for gestational age, there was no significant difference in birth weight compared to the control population. This indicated that these mothers did not tend to bear low birth weight babies before poisoning.

Adjusting for gestational age, the birth weight of transplacental Yu-Cheng babies was significantly lower than that of the control population at the 1st, 2nd

Table 1. Birth status of 130 transplacental Yu-Cheng babies born to 78 PCB-poisoned mothers from 1979 to 1986.

Variables	Male	Female	Total
Number of cases	66	64	130
Gestational Week			
Mean±SD	38.9±2.7	39.3±1.7	39.1±2.3
Birth weight (gm)			
Mean±SD	2734±558	2712±429	2723±497
Low Birth Weight (<2500gm)	27.3%	28.1%	27.7%
Premature (<=37 week)	30.3%	18.8%	24.6%

and 3rd gravidity after poisoning, but not at the subsequent gravida. There was a tendency for later gravida to attain a higher Z score (Figure 1). It meant the birth weight of Yu-Cheng babies improved in later gravida.

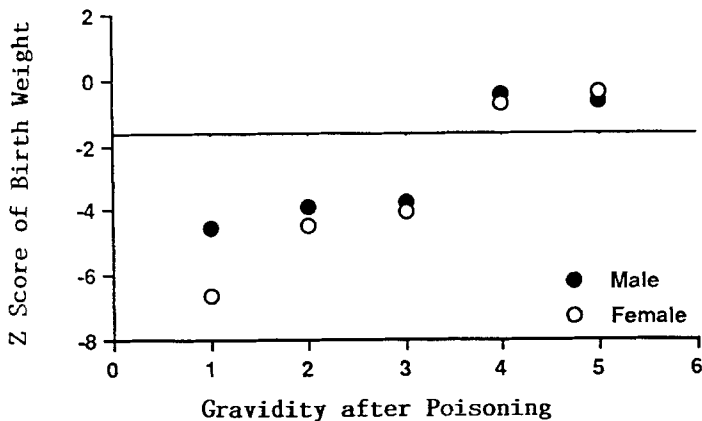


Figure 1. Z score of birth weight of transplacental Yu-Cheng babies by sex and gravidity after poisoning ( $p=0.05$ , if  $Z \text{ score} = -1.645$ ).

Except for male babies in 1979, the birth weight of Yu-Cheng babies born shortly after the poisoning episode was significantly lower than that of the control population. This situation improved starting in 1985, 6 years after the episode (Figure 2).

The birth weight of Yu-Cheng babies improved over time

Table 2. Birth weight (gm) and gestational week of 17 babies born to PCB-poisoned mothers before poisoning in January, 1978.

Male Babies				Female Babies			
Birth Weight (gm)	Gestational Week	Control population* (Mean±SD) (gm)	Z Score	Birth Weight (gm)	Gestational Week	Control population* (Mean±SD) (gm)	Z Score
2900	40	3301±389	-1.03	3100	40	3173±368	-0.20
3000	40	3301±389	-0.78	2800	40	3173±368	-1.01
2080	35	2420±450	-0.76	3000	40	3173±368	-0.47
2900	40	3301±389	-1.03	3300	39	3085±363	0.59
3100	40	3301±389	-0.52	4000	40	3173±368	2.25
3150	40	3301±389	-0.39	3300	40	3173±368	0.35
3500	40	3301±389	0.51	3200	40	3173±368	0.07
3600	40	3301±389	0.77	3200	38	2976±387	0.58
3700	40	3301±389	1.03				
$Z = (\sum z_i) / \sqrt{n} = -2.20 / \sqrt{9} = -0.73$				$Z = (\sum z_i) / \sqrt{n} = 2.16 / \sqrt{8} = 0.76$			

\* Data were from the birth weights of same sex and gestational weeks of babies delivered in a teaching hospital (male 18865; female 17054).

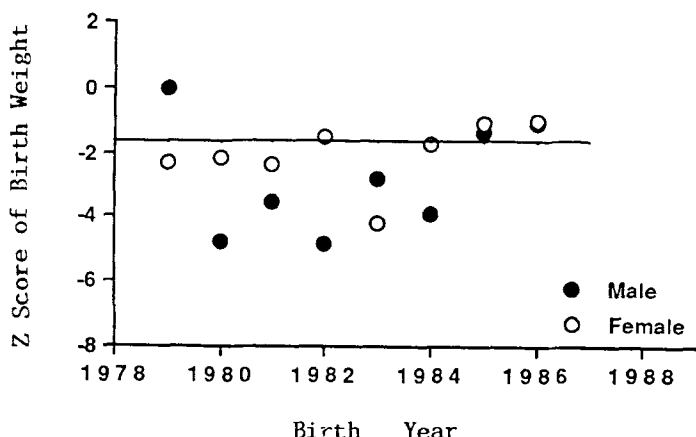


Figure 2. Z score of birth weight of transplacental Yu-Cheng babies by sex and birth year.  
( $P=0.05$ , if  $Z \text{ score}=-1.645$ )

for all gravidity levels. From 1985 on, there was no significant difference from the control population. For the 3rd and later gravidity improvement was observed starting 1983 (Figure 3).

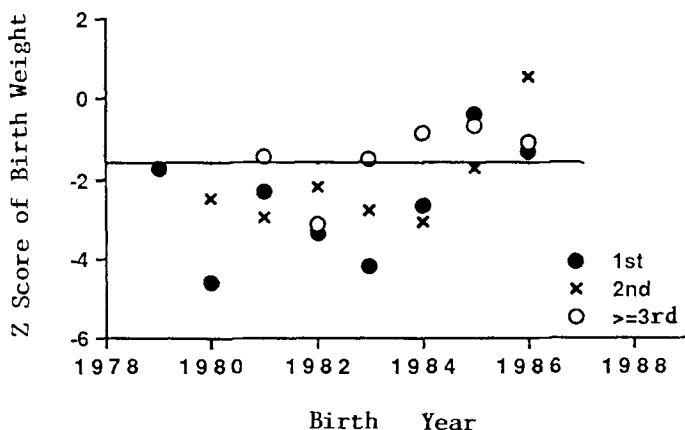


Figure 3. Z score of birth weight of transplacental Yu-Cheng babies by gravidity and birth year.  
( $P=0.05$ , if  $Z \text{ score}=-1.645$ )

Our studies indicated that, for a baby who was conceived during the first few years after the mother's poisoning, the intrauterine growth was retarded. Identical results were seen for the few cases studied in Japan (Yamagushi 1971). Moreover, after following-up of these poisoned women over a longer period of time, we found that, as the

time elapsed and the gravidity after poisoning increased, the intrauterine growth of transplacental Yu-Cheng babies had improved. This result is also in agreement with other studies that had fewer cases and shorter follow-up time period (Yoshimura 1974; Lan 1982). The improvement of intrauterine growth of Yu-cheng babies might be evidence of the reduced maternal body-burden of PCBs and PCB-thermal derivatives over time. The half-lives of PCDFs and PCBs in blood are 2.14-2.56 and 1.16-4.56 years, respectively (Masuda et al. 1991). According to these estimates, the PCDFs and PCBs body-burden of the poisoned mothers in 1985 were lower than 1/8 of the initial concentration. Pregnancy and breast-feeding will let PCBs and PCDFs excrete more easily; with these activities the body-burden may be even lower. For this reason, fetuses from later (in time or in gravidity) pregnancies of PCB-poisoned women may be less affected by PCBs.

High infant mortality rate ( $8/39=205$  per 1000 Yu-Cheng infants) among pigmented-skin transplacental Yu-Cheng babies followed to 1983 had been reported. Another study reported a mortality of 110 per 1000 Yu-Cheng infants (18/163) among transplacental Yu-Cheng babies followed to 1986 (Yen 1990). This might be due to premature birth or low birth weight or both. However, even though these Yu-Cheng babies had a lower birth weight, their body weight increased sufficiently to catch up with the general population in early childhood (Yen et al. 1989).

We previously reported that female transplacental Yu-Cheng babies had more congenital missing of permanent teeth (Lan et al. 1989). Rogan et al. (1987) indicated that they have had more bronchitis or pneumonia, pigmented or deformed nails, and growth retardation in early childhood. The most harmful effects occur among the Yu-Cheng babies conceived in the first pregnancy shortly after poisoning. The incidence of poor pregnancy outcomes decreased as time elapsed and higher birth order was attained after poisoning. We therefore concluded that (1) PCB-poisoned women should avoid pregnancy and breast feeding in the 3-5 years after poisoning, (2) Detailed investigations of neurologic and immunologic function should be conducted on transplacental Yu-Cheng babies who were first born or born within 5 year of their mothers' PCBs poisoning episode (Rogan et al. 1987; Lan et al. 1989/1990; Yu et al. 1991).

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## REFERENCES

Chen PH, Wong CK, Rappe C, Nygren N. (1985) Polychlorinated biphenyls, dibenzofurans and quaterphenyls in

- toxic rice-bran oil and in the blood and tissues of patients with PCBs poisoning (Yu-Cheng) in Taiwan. *Environ Hlth Perspect* 59:59-65.
- Department of Health, Executive Yuan. (1987) Health statistics: 2. Vital statistics, 1986. Republic of China.
- Escalona SK. (1982) Babies at double hazard : Early development of infants at biologic and social risk. *Pediatrics* 70:670-676.
- Funatsu I, Yamashita F, Yoshikame T, funatsu T, Ito Y, Tsugawa S, Kato T, Yakushiji M, Okamoto G, Arima A, Adachi N, Takahashi K, Miyahara M, Tashiro Y, Shimomura M, Yamasaki S, Arima T, Kuno T, Ide H, Ide I. (1971) A chlorobiphenyls induced fetopathy. *Fukuoka Acta Med* 62:139-149.
- Harvey D, Prince J, Bunton J, Parkinson C, Campbell S. (1982) Abilities of children who were small-for-gestational age babies. *Pediatrics* 69:296-300.
- Hogg RV, Craig AT. (1978) Distribution of functions of random variables. In : Introduction to mathematical statistics, 4th ed. Macmillan Publ. Co., New York, 176-179.
- Hsu ST, Ma CI, Hsu SKH, Wu SS, Hsu NHM, Yeh CC, Wu SB. (1985) Discovery and epidemiology of PCBs poisoning in Taiwan: A four-year follow up. *Environ Hlth Perspect* 51:5-10.
- Kodama H, Ota H. (1980) Transfer of polychlorinated biphenyls to infants from their mothers. *Archives Environ Health* 35:95-100.
- Lan SJ. (1982) PCBs poisoned mothers and their babies. MPH thesis of Medical College of National Taiwan University.
- Lan SJ, Yang CY, Yang CH, Yen YY. (1987) 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, Yen YY, Ko YC, Chen ER. (1989) Growth and development of permanent teeth germ of transplacental Yu-Cheng babies in Taiwan. *Bull Environ Contam Toxicol* 42:931-934.
- Masuda Y, Kagawa R, Kuroki H, Kuratsune M, Kuratsune M, Yoshimura T, Taki I, Kusuda M, Yamashita F, Hayashi M. (1978) Transfer of polychlorinated biphenyls from mothers to fetuses and infants. *Fd Cosmet Toxicol* 16:543-546.
- Masuda Y, Kuroki H, Haraguchi K, Ryan JJ, Shu ST. (1991) Elimination of PCDF congeners in the blood of patients with PCB poisoning in Taiwan. *Fukuoka Acta Med* 82:262-268.
- Rogan WJ, Gladen BC, Hung KL, Koong SL, Shih LY, Taylor JS, Wu YC, Yang D, Rogan NB, Hsu CC. (1987) Congenital poisoning by polychlorinated biphenyls and their contaminants in Taiwan. *Science* 241:334-336
- Susser M, Marolla FA, Fleiss J. (1972) Birth weight,



- fetal age and perinatal mortality. *Am J Epidemiol* 96:197-204
- 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.
- Yen YY, Lan SJ, Ko YC, Chen CJ. (1989) Follow-up study of reproductive hazards of multiparous women consuming PCBs-contaminated rice oil in Taiwan. *Bull Environ Contam Toxicol* 43:647-655.
- Yen YY, Lan SJ, Lu CT, H SF, Ko YC. (1990) Frequency distribution of birthweight and gestational age in Taiwan. *Kaohsiung J Med Sci* 3:372-276.
- Yen YY. (1990) Follow-up studies on reproductive hazards of PCB-poisoned women. PhD. Thesis of Graduate Institute of Medicine, Kaohsiung Medical College, p47-48.
- Yoshimura T. (1974) Epidemiological study on Yusho babies born to mothers who had consumed oil contaminated by PCBs. *Fukuoka Acta Med* 65:74-80.
- Yu ML, Hsu CC, Gladen BC and Rogan WJ. (1991) In utero PCB/PCDF exposure: relation of developmental delay to dysmorphology and dose. *Neurotoxicol Teratol* 13:195-202.