

Intellectual Development in Children Whose Mothers Received Propylthiouracil During Pregnancy

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Received July 18, 1977

Standard intelligence tests were administered to twenty-eight children who had been exposed to PTU in utero and thirty-two non-exposed siblings. There was no significant difference in results between the two groups. The present study suggests that with careful attention, pregnant women with thyrotoxicosis can be treated with propylthiouracil without interfering with subsequent intellectual development in the offspring.

Recent interest in neonatal screening for congenital hypothyroidism has refocused interest on hypothyroidism during the perinatal period [1,2,3]. Thyrotoxicosis has an incidence of about two per 1,000 pregnancies and children born to thyrotoxic mothers treated with propylthiouracil during pregnancy are at risk for the development of perinatal hypothyroidism. Although cretinism is uncommon after PTU [4], the possibility exists that such offspring do not live up to their full intellectual potential because of some degree of hypothyroidism in utero. In a previous study we compared the intellectual development of children who had been exposed to PTU in utero to non-exposed siblings [5]. The data did not suggest that PTU therapy during pregnancy had an adverse effect on subsequent growth and development of a child, but the sample was small.

In view of the clinical importance of determining the potential effect of thiouamides on the intellectual development of the fetus, 23 mothers were identified who had received propylthiouracil (PTU) for thyrotoxicosis due to Graves' disease during pregnancy. These mothers had a total of 65 children. Because of availability, 60 children ranging in age from 2 to 28 years were studied. Twenty-eight children had been exposed to PTU in utero (11 females and 7 males); 32 siblings served as non-exposed controls (18 females and 14 males). With six exceptions each child who had been exposed to PTU in utero had at least one sibling in the control group. Of the 17 women having both exposed and non-exposed children, in 9 cases the exposed children were in birth order the oldest of the siblings studied, in 6 they were the youngest, and in 2 they held an intermediate position in a large family.

Of the 28 children exposed to PTU in utero, 23 children had been exposed to the drug at least during the last trimester. One child had been exposed to the anti-thyroid compound during the second trimester only and three during the first trimester only; no data on the period of exposure during pregnancy was available in one child.

Eleven children were exposed to 300 mg of PTU or more at some time during gestation and four of these children were exposed to 400 mg or more of PTU.

Because of the age range of the subjects, it was not possible to administer the same intelligence test to the entire group. In the experimental group, 8 subjects were given the Wechsler Preschool and Primary Scale of Intelligence, 16 were given the Wechsler Intelligence Scale for Children (Revised), one was given the Wechsler Adult Intelligence Scale, two were given the McCarthy Scales of Children's Abilities, and one was given the Stanford-Binet. In the control group, one subject was given the Stanford-Binet, two were given the Wechsler Preschool and Primary Scale of Intelligence, 26 were given the Wechsler Intelligence Scale for Children (Revised), and three were given the Wechsler Adult Intelligence Scale.

RESULTS

Figure 1 shows the distribution of intelligence quotients for the two groups, expressed in standard deviation units from the mean of the test ($M = 100$, $SD = 15$). Figure 2 gives the distribution of Verbal IQ and Performance IQ for those subjects who were old enough to be given a form of the Wechsler Scales, also expressed in standard deviation units from the mean. (The Binet and McCarthy do not lend themselves to this latter type of analysis.)

Two types of statistical analysis were performed on the data. The median test [6, pp. 111-112] was applied to the total population of 60 subjects, and a paired- t comparison [7, p. 335] was made between the siblings of the women having both exposed and non-exposed children.

The median IQ for the total group of 60 subjects was 100, with a range from 50 to 132 in the experimental group and from 53 to 122 in the control group. Using Chi-squared applied to the median test, the difference between the groups was not significant ($X^2 = 1.08$, $p < .30$).

For the 56 children who received some form of the Wechsler Scales, the median Verbal IQ was 96, with a range from 57 to 133 in the experimental group and from 55 to 122 in the control group. Applying Chi-squared to the median test, the difference was not significant ($X^2 = 1.16$, $p < .30$).

The median Performance IQ for the group of 56 children was 103, with a range

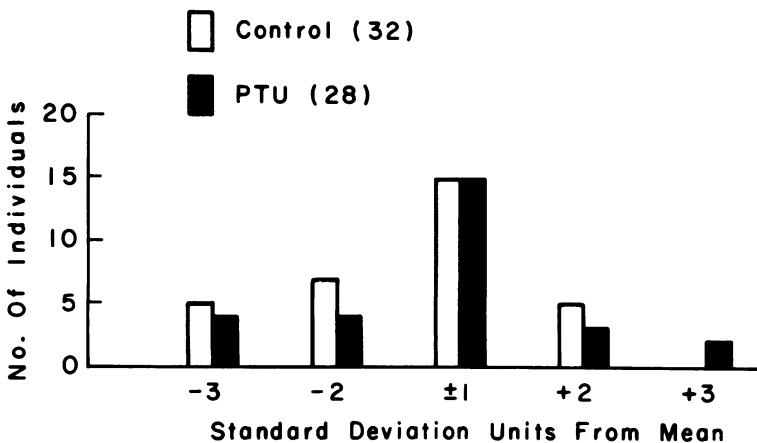


FIG. 1. Distribution of Intelligence Quotients Expressed in Standard Deviation Units from the Mean ($M = 100$, $SD = 15$ points).

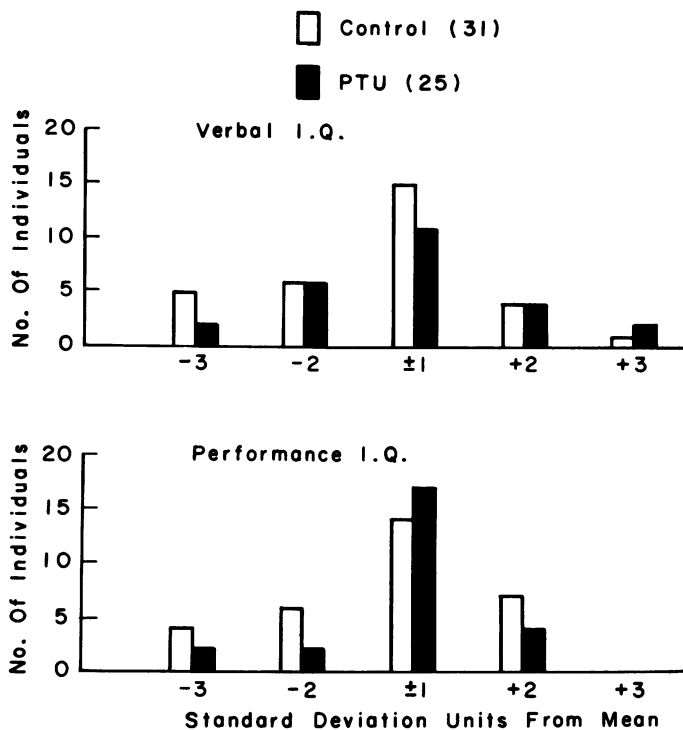


FIG. 2. Distribution of Verbal IQ and Performance IQ on the Wechsler Scales.

from 51 to 135 in the experimental group and 57 to 129 in the control. The value of Chi-squared applied to the median test was again insignificant ($X^2 = 0.29, p. < .90$).

Second, a paired- t test was computed between the siblings of the 17 women with children in both the control and experimental groups. In order to establish pairs for comparison, it was necessary to average the IQ ratings of the children where there was more than one sibling in either the control or experimental group. For example, in one instance a woman had two children in the experimental group and four in the control group. When pairs were established in this manner, the mean of the differences between the 17 pairs was zero and therefore t was zero.

A paired- t test was then computed between the siblings of the 15 women with children in both control and experimental groups who had been given some form of the Wechsler Scales. Paired- t for the difference between the groups in Verbal IQ was insignificant ($t = 0.51$) as was the difference in Performance IQ ($t = 0.29$).

Six children were goitrous at birth; two children had neonatal thyrotoxicosis while the other four were thought to be goitrous presumably because PTU had crossed the placenta and blocked the fetal thyroid with secondary stimulation of fetal TSH (Table 1). The presence of goiter implied that these children had been hypothyroid at some period during gestation. The mean IQ for the goitrous children who did not have neonatal thyrotoxicosis was 102 ± 8 (\pm SD). Both infants with neonatal thyrotoxicosis had a significant depression in IQ. However, there is no evidence that Graves' disease per se is related to retarded intellectual development in offspring. In the case of the children with toxic goiter, the five siblings of L.P. had IQ's of 61, 66, 74, 81, and 81. The one sibling of P.C. had an IQ of 100.

The 11 children who had been exposed in utero to 300 mg of PTU per day or more

TABLE I
Goitrous Offspring of Mothers Receiving Propylthiouracil

Name	Maternal Drug Therapy During 3rd Trimester	Birth Weight: Baby	Sex	LATS Mother %	LATS Baby %	Maternal T4 (l) at Delivery μ g/dl	Cord Blood T4 (l) μ g/dl	Neonatal T4 (l) 24 hr Post Delivery μ g/dl	Maternal Thyroid Status During Pregnancy	IQ of child	Neonatal Therapy
Non-Toxic Goiter C.P.	150 mg PTU	2700	Female			PBI 9.2	PBI 7.4	T4I (c) 4.1	Euthyroid	87	
P.S.	300 mg PTU, 50 mg KI	3215	Male					PBI 1.9	Hyper-thyroid	122	Thyroid Hormone 6 months
S.W.	100 mg PTU, 50 mg KI	2780	Female			BEI 6.1	BEI 3.5	BEI 1.9	Hypo-thyroid	88	Thyroid Hormone 9 months
G.W.	150 mg PTU, 50 mg KI	3030	Male			BEI 11.0		BEI 1.6	Euthyroid	122	Thyroid Hormone 12 months
Toxic Goiter L.P.	200 mg PTU	1930	Female	779	509	T4I (c) 10.7	T4I (c) 12.7		Euthyroid	67	PTU 1 month
P.C.	150 mg PTU 2 gr thyroid	3525	Male	335			PBI 11	PBI 11.3	Hypo-thyroid	79	Became mildly Toxic 5 days after birth
Normal Values		Maternal (μ g/dl)						Cord (μ g/dl)			
		PBI 6.5-11.5						4.0-9.5			
		BEI 5.5-10.5						4.0-9.5			
		T4I 5.5-10.5						4.0-9.5			

had a mean IQ of 85 ± 8 (\pm SD), which was not significantly lower than the PTU-treated group as a whole. Five children in this group had an IQ less than 80.

DISCUSSION

There was no difference in intelligence test results between children exposed to PTU in utero and their non-exposed siblings. Those results confirm and extend the previous findings on a smaller group of exposed children [5]. In the previous study the younger children were tested with a variety of developmental tests and the results were difficult to compare with one another.

On the basis of the present study, PTU can be used in the treatment of thyrotoxicosis during pregnancy without major concern that subsequent intellectual development will be affected significantly. Clearly, it is important that the mother not be overtreated, with the induction of maternal and fetal hypothyroidism. Every effort should be made to keep the maternal dose of PTU as low as possible; maternal hypothyroidism should be treated promptly with thyroid hormone.

Six children who had been exposed to PTU had neonatal goiter. Two of these children had neonatal thyrotoxicosis while four had non-toxic goiter. All four children were hypothyroid at birth although maternal thyroid values were normal. Three of the four children with non-toxic goiter were also exposed to iodides which has been associated with neonatal goiter independently of anti-thyroid therapy [8]. These three children also received thyroid hormone therapy shortly after birth which complicates the interpretation of their subsequent intellectual development.

Some clinicians have recommended surgery as the treatment of choice for the pregnant thyrotoxic woman, in part because of the possibility of mental retardation associated with PTU therapy [9]. However, results of the present study indicate that pregnant women with thyrotoxicosis may be treated with PTU without interference with subsequent intellectual development in the offspring.

ACKNOWLEDGEMENTS

The study was supported in part by the Yale Children's Clinical Research Center, supported by Grant RR-00125 from the GCRC Branch, Division of Research Resources, National Institutes of Health, Bethesda, Maryland, and by the National Foundation March of Dimes.

We would like to thank Mrs. Mary Estabrook and Mrs. Jessie Beal for testing some of the children, and Terri Pechinski, R.N., for valuable assistance.

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