

# Effects of maternal iodine supplementation during pregnancy

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## Abstract

**Reduced maternal thyroid hormone concentrations during pregnancy can adversely affect fetal neurological development. In the context of national iodine supplementation programmes, concern has been expressed over the theoretical possibility that iodine supplementation during pregnancy might adversely affect fetal development as a result of maternal thyroid inhibition from the Wolff-Chaikoff effect. In a double blind controlled trial in five villages in Papua New Guinea, several measures of motor and cognitive function showed no significant differences at either age 11 or 15 years between those children whose mothers had received supplementary iodine during pregnancy and the control children whose mothers had received the placebo.**

Iodine deficiency is a worldwide problem that leads to clinical goitre and the syndrome of endemic cretinism together with subclinical deficits of motor and cognitive function. This spectrum of defects has been collectively labelled iodine deficiency disorder.<sup>1</sup> Prevention of iodine deficiency disorder by iodine supplementation is known to be effective but, in the case of endemic cretinism, supplementation must be before conception because the neurological damage due to iodine deficiency appears to occur early in fetal development.<sup>2</sup> Because iodine supplementation is a relatively cheap and highly effective preventive measure, national programmes of iodine supplementation have been initiated in several countries where iodine deficiency disorder show high prevalence rates. One method of supplementation has been the use of a single dose of iodinated oil by either oral or intramuscular administration. When a single dose is used, the quantity given is substantial, although absorption is slow. The iodine concentration in the oil is approximately 475 mg/ml and doses of up to 5 ml have been used.<sup>3</sup> Failure of normal fetal neurological development attributed to maternal iodine deficiency is thought to be mediated through a reduction of maternal thyroid hormone concentrations and specifically maternal thyroxine.<sup>4-6</sup> Excess iodine administration may lead to an acute inhibition of the thyroid, a phenomenon termed the Wolff-Chaikoff effect after the workers who originally described it.<sup>7</sup> Concern has therefore been raised that administration of iodine during pregnancy may also affect fetal neurological development if it leads to maternal thyroid gland inhibition by the Wolff-Chaikoff effect.<sup>8</sup> This anxiety has

imperilled some national iodine prophylactic programmes.

During 1966 a double blind controlled trial using a single dose of intramuscular iodinated oil was carried out in the Western Highlands of Papua New Guinea. In the course of this trial several pregnant women were given iodine at various gestational stages. We report here a long term follow up of these pregnancies using measures of mental and motor function to assess the development of the children.

## Methods

The organisation of the controlled trial initiated in the autumn of 1966 has been described previously.<sup>2</sup> In 1978 a follow up was carried out of the cohort of children born to the trial group. The children of mothers who had received iodinated oil constituted the test groups and those of mothers who had received the placebo of physiological saline constituted the control group. Those children born within 40 weeks of the mother receiving either iodinated oil or saline are the index cases for this report. In these cases the mother was assumed to have conceived before the iodinated oil or saline was administered. In 1978, when the index children were approximately 11 years old, several measures of physical and motor performance were applied. These included grip strength, speed of movement, unimanual accuracy, and bimanual accuracy. The methods of carrying out these tests and the scoring procedures have been described previously.<sup>9</sup> For all these measures except that involving the application of screws to bolts the score correlates positively with level of skill—that is, the higher the score the greater the skill. The screwing task was a timed measure and therefore correlates negatively with manual dexterity—that is, the lower the score the greater the dexterity.

In 1982, when the children were approximately 15 years old, a further series of measures of motor and cognitive ability were applied. Some of the unimanual and bimanual measures of manual dexterity used in 1978 were repeated because they had been found to discriminate well for motor performance.<sup>9</sup> In addition, a further test of motor skill was employed that required the subject to transfer a series of 10 one cm pegs from one set of holes in a frame to another set 20 cm away in the frontal plane. The time required for the transfer was measured with a stopwatch. Five repetitions with each hand were made and the score used in the analysis was the mean time required to transfer

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10 pegs. (The shorter the time taken the greater the skill.) In 1982, an attempt was also made to assess the intellectual performance of the children using the Pacific design construction test (PDCT) developed by Ord and used in Papua New Guinea to select army recruits and young people for technical training.<sup>10</sup> The test comprises 13 designs of varying complexity printed on cards. The subject is required to make a copy of each design in tiles (red, white, and red and white) in a set of specially shaped trays. The score is based upon producing correct copies within defined time periods. A preliminary trial of children from the study area, but who were not themselves part of the index sample, showed that they experienced great difficulty in translating the printed design into a model made from the tiles. This difficulty probably reflects their unfamiliarity with pictures. The testing procedure was therefore modified in the following way. The examiner constructed the design tiles in one tray while the subject watched. The subject was then invited to reproduce the design in an adjacent tray. The

model was available to the subject throughout the trial. The test was administered in a manner that relied largely on non-verbal instructions though these were supplemented by verbal instructions translated into pidgin English for use in the field.

Standing height was measured using a Harpenden portable anthropometer.

Statistical comparisons of the two groups of children were made using Student's *t* test.

## Results

The original 1966 trial was carried out in 27 villages and involved approximately 8000 individuals in each of the test and control groups.<sup>2</sup> Subsequent follow up of the children born into the trial population had to be limited to a more confined group of villages for logistic reasons only. In 1978 and 1982 the follow up was limited to five villages.

Table 1 compares the scores achieved by the two groups of children in 1978 when they were 11 years old. In none of the measures of motor

Table 1 Comparison of scores for test and control groups in 1978

Motor competence measure	Test (iodinated oil)		Control (placebo)		Difference between means (95% confidence intervals)	p Value
	No	Mean (SE)	No	Mean (SE)		
Grip strength:						
Right hand	12	11.8 (0.6)	17	12.4 (0.7)	-0.6 (-2.5 to 1.3)	0.46
Left hand	12	11.4 (0.5)	17	11.9 (0.6)	-0.5 (-2.1 to 1.1)	0.59
Speed of movement:						
Taps						
Right hand	12	37.9 (1.8)	18	37.3 (2.1)	+0.6 (-4.9 to 6.1)	0.82
Left hand	12	35.4 (1.7)	18	36.3 (2.2)	-0.9 (-6.5 to 4.6)	0.76
Dots (mean of four trials)	12	21.6 (0.8)	18	21.8 (1.2)	-0.2 (-3.0 to 2.6)	0.89
Bimanual accuracy:						
Beads	11	17.2 (1.0)	17	15.3 (0.9)	+1.9 (-0.8 to 4.6)	0.17
Unimanual accuracy:						
Pegs	12	23.3 (1.4)	18	20.5 (1.2)	+2.8 (-0.9 to 6.5)	0.15
Screws	12	71.9 (7.3)	17	80.8 (10.1)	-8.9 (-34.0 to 16.2)	0.48

The differences between mean test results are positive or negative and the meaning of directional changes for each test is explained in the text.

Table 2 Comparison of scores for test and control groups in 1982

Motor competence measure	Test (iodinated oil)		Control (placebo)		Difference between means (95% confidence intervals)	p Value
	No	Mean (SE)	No	Mean (SE)		
Grip strength:						
Right hand	13	16.6 (0.8)	15	16.8 (1.2)	-0.2 (-3.2 to 2.8)	0.90
Left hand	13	15.9 (0.7)	15	15.9 (1.1)	0.0 (-2.0 to 2.0)	0.99
Bimanual accuracy:						
Beads	13	17.2 (1.3)	16	17.1 (1.3)	+0.1 (-3.5 to 3.7)	0.96
Unimanual accuracy:						
Pegs	13	25.4 (1.1)	16	24.6 (1.4)	+0.8 (-2.9 to 4.5)	0.66
Peg frame						
Right hand	13	13.0 (0.8)	16	14.3 (1.3)	-1.3 (-4.5 to 1.9)	0.41
Left hand	13	13.5 (0.9)	16	14.4 (1.2)	-0.9 (-3.9 to 2.1)	0.53
Cognitive task:						
PDCT	13	12.8 (2.1)	15	12.0 (2.0)	+0.8 (-5.0 to 6.6)	0.77
Height	13	135.1 (1.9)	16	135.1 (2.2)	0.0 (-5.9 to 5.9)	0.998

The differences between mean test results are positive or negative and the meaning of directional changes for each test is explained in the text.

performance taken was a significant difference between the two groups of children observed. In four measures (grip strength right hand, grip strength left hand, dots and number of taps right hand) the control group performed marginally better. In the remaining four measures (taps left hand, beads, screws, and pegs) the test group of children had higher scores.

Table 2 compares the scores achieved in 1982. On this occasion in addition to the motor indices, it was possible to compare also cognitive function as measured by the PDCT and height. None of the measures showed a significant difference between the two groups. The cognitive and all five tasks of motor skill marginally favoured the test group of children while the index of hand strength marginally favoured the control children.

### Discussion

The fears that administering iodine during pregnancy may compromise fetal development as a consequence of maternal thyroid inhibition via the Wolff-Chaikoff effect may be allayed by the data presented here. The relatively small number of children in this study inevitably raises the possibility of a type II statistical error. Even this is unlikely, however, as most measures employed both in 1978 when the children were aged 11 and in 1982 when they were aged 15, favoured the test group more often than the controls. It is pertinent that the measures that most nearly approached significance were the bead threading and pegboard tests in 1978. These measures proved the most discriminating when applied to all the children in the trial reported previously.<sup>9</sup>

In the trial reported here 4 ml of iodinated oil were given to the test group of mothers during pregnancy whereas current World Health Organisation recommendations are for smaller amounts to be administered (1–2 ml),<sup>3</sup> thus further reducing the risk of thyroid inhibition.

Furthermore, the Wolff-Chaikoff effect was demonstrated in iodine replete rats; that a similar inhibition of the thyroid gland follows iodine administration to an iodine deficient human population has not been demonstrated.

In contrast to the clear evidence that maternal iodine deficiency may severely compromise the development of the fetus, there is no evidence that the administration of iodine at recommended dose levels has any deleterious effect. Although it is necessary to keep a constant watch for any complication arising from the mass prophylaxis of iodine deficient populations, all the available evidence points to a highly advantageous benefit to risk ratio.

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