Effects of iodine supplementation during pregnancy on child growth and development at school age

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Growth and development of 207 children (49% males; mean age 5.4 years [SD 0.2], range 4 to 7.3 years whose mothers received iodine during pregnancy, and children who received iodine first in their 2nd year, were examined in 1996; 192 children (49% males; mean age 6.5 years [SD 0.2], range 5.8 to 6.9 years) whose mothers received iodine while pregnant were seen in 1998. Children were from the southern part of China's Xinjiang Province which has the lowest levels of iodine in water and soil ever recorded. Head circumference but not height was improved for those who received iodine during pregnancy (compared with those receiving iodine at age 2) and for those supplemented before the end of the 2nd trimester (relative to those supplemented during the 3rd trimester). Iodine before the 3rd trimester predicted higher psychomotor test scores for children relative to those provided iodine later in pregnancy or at 2 years. Results from the test for cognitive development resulted in trend only differences between those children supplemented during pregnancy versus later. The results address the question of when maternal iodine supplements should begin in public health programs world wide. Findings may be relevant to the treatment of maternal and newborn thyroid deficiency in industrialized countries, particularly for those infants delivered before the end of the second trimester.

Endemic congenital hypothyroidism in the offspring of women with severe iodine deficiency during pregnancy is considered the world's most prevalent preventable cause of mental retardation* (Stanbury and Hetzel 1980, Dunn 1993). Congenital severe hypothyroidism (CSH) is characterized by a coherent clinical picture of psychological deficiency, neurological abnormalities, hearing loss, and poor growth (DeLong et al. 1985). Associated intellectual problems generally fall in the range of moderate to severe and are evident in cognitive and perceptual motor functioning. A condition sometimes called subcretinism refers to the mild to moderate cognitive and motor deficiencies found in the general population in regions where there is iodine deficiency, suggesting that the effects of maternal iodine deficiency on children form a continuum ranging from mild to severe developmental disability (e.g. Ma 1988, Ma et al. 1989).

The association between an iodine-deficient region and a range of developmental deficits in children and adults is well accepted but not well documented (Connolly and Pharoah 1993). Furthermore, the pathophysiology and timing of the in utero CNS injury have not been explored completely. There is evidence from our work (Cao et al. 1994b) and that of others of a sensitive period in pregnancy when maternal iodine deficiency affects the developing fetal brain. Our data suggest that iodine supplements for pregnant women should occur before the end of the second trimester, to reduce the incidence of CSH and, in general, improve growth and development in their children.

People in areas with iodine deficiency, in both developing and industrialized countries, are dependent on iodine supplementation by iodized salt, injections of iodinated oil, oral iodine administration, or other methods. The success of supplementation is often determined by an array of geographical, economic, cultural, political, and/or religious factors. Xinjiang autonomous region, a large northwest province in the People's Republic of China, has severe iodine deficiency related to the geography of the large Taklamakan Desert on an alluvial plain near the Kunlan Mountains. The majority of the population in the region belong to the Uighur minority group. The Uighurs are Muslims, many of whom are peasants living in villages around the desert. The land, which supports subsistence farming and sheep, has the lowest levels of iodine in water and soil ever recorded. Unpublished data available from Xinjiang Autonomous Region Endemic Health Department indicates that the iodine content in water is 1.2 μg/L (0.01 μmol/L) and in soil is 7 to 240 μg/kg (0.06 to 1.9 μmol/kg). The local inhabitants prepare food with rock salt obtained from the desert, preferred because it is free and described as more savory than iodized salt.

The southern rim of the Taklamakan Desert, with a population of 1.2 million, had a visible goiter prevalence of 54% and CSH rates at 2% in our 1990 survey (Cao et al. 1994b). Therefore, successful methods of effective iodine provision are important for the prevention of CSH, for the development of the children in the region, and for improving the educational and economic well-being of the population in general.

In 1990, our group designed a series of studies to test whether treatment with iodine during gestation and in early childhood would lead to improved growth and neurodevelopment compared with iodine supplementation later in life.

*North American usage; UK: learning disability.

Findings from these studies are described in detail in previous reports (e.g. Cao et al. 1994b, DeLong et al. 1998). In summary, a large cohort of pregnant women and young children were recruited and given oral iodine. Head growth, neurological status, and achievement of developmental milestones were assessed when the children were approximately 6, 12, and 24 months old. The comparison group comprised children who were examined first at their initial iodine supplement at 2 years of age. The benefits of providing early iodine supplements during gestation, particularly before the end of the second trimester, were documented. No cases of frank CSH were identified. The frequency of microcephaly and neurological dysfunction was significantly reduced for those children treated before the end of the second trimester relative to those treated later in pregnancy or from two years of age.

The Bayley Scales of Infant Development (Bayley 1969) were used when the children were 2 years of age. A few items were deleted from the Bayley Scales for cultural reasons. However, test items were arranged for ease of administration so that the examiner performed all items using a specific test material at once. For example, all age-appropriate items with red cubes were administered together. Test results indicated that children treated during pregnancy had higher developmental scores than those not treated until 2 years ($p<0.01$) and that those treated before or during the 2nd trimester were significantly higher than those treated later in pregnancy ($p<0.001$; O'Donnell et al. 1994).

The present report examines the relationship between the timing of iodine supplementation during gestation and early childhood and growth and development at school age.

Method

PARTICIPANTS

The longitudinal study originally included 689 children (169 of whom were in the 2-year-old comparison group) and 295 pregnant women recruited in 1990. Children were grouped according to age at first iodine supplement (Table I). Forty-nine percent of all participating children were male.

For the school-age follow-up studies, all eight villages from Tusala township, which had participated in the previous follow-up study (Cao et al. 1994b), were included. Upon the arrival of the research team in the village, children who were first supplemented during pregnancy or at 2 years were called to the village center by the community loud speaker. There is no reason to think that the parents and children who came to participate in the follow-up studies were self-selected in any way that would affect the results.

The comparison group was identified and treated at age 2 years. At the same time, the pregnant women were identified and treated. There were no untreated participants. Thus, those children treated in utero were about 2 years younger than the comparison children. For the school-age follow-up studies, all children were seen either in 1996 or 1998, as close to 6 years of age as was practical. The comparison group and those treated during pregnancy are thought to have had adequate iodine nutrition after the initial treatment. The children from the pregnancy groups received treatment at 6, 12, and 24 months, and those treated first at 2 years would be protected for 1 year or more. At that time, iodine supplementation was carried out by adding it to the irrigation water (Cao et al. 1994a).

Of the comparison group treated first at 2 years of age, 70 (47%) of the original group participated in the 1996 follow-up testing in 1996 (see Table I). Of those children treated during pregnancy, 127 (43%) were tested in 1996; 192 (65%) were seen in 1998 (see Table I). Approximately 100 children were seen on both occasions.

The study was approved by Duke University Medical Center's Internal Review Board for Research with Human Subjects; all parents provided oral, informed consent. Uighur physicians and local Uighur health personnel worked with the study team at all times.

PROCEDURE

This report includes data on the growth and psychological development of children examined in September 1996 and May 1998, when they were between 5 and 7 years old. Growth and developmental differences between groups determined by the timing of the first iodine supplement were examined; pregnancy trimester groups were compared

Table I: Number (%) and ages (mean, SD, range) of children from original group participating in follow-up studies

Group	*At initial iodine dose*	*Follow-up in 1996*	*Ages (y) in 1996*	*Follow-up in 1998*	*Ages (y) in 1998*
First trimester	48	14 (29)	4.8 (0.23) 4–4.9	23 (48)	6.2 (0.21) 5.8–6.4
Second trimester	99	43 (43)	5.5 (0.18) 4.5–5.8	66 (67)	6.4 (0.22) 5.9–6.8
Early pregnancy[a]		*57 (39)*	*4.9 (0.24)* *4–5.8*	*89 (61)*	*6.3 (0.25)* *5.8–6.8*
Third trimester	148	70 (47)	5.2 (0.22) 4.9–5.4	103 (70)	6.7 (0.15) 5.9–6.9
Comparison group. 24–36 mo	169	80 (47%)	6.7 (0.36) 5.4–7.3		
Totals	464	207		192	

[a]1st and 2nd trimester were combined as 'early pregnancy' due to the small number of children seen in the 1st trimester; not included in totals.

with one another and with the comparison group. As the 1996 study in particular included a small number of children from the group supplemented in the first trimester (14 in 1996 and 23 in 1998), the children from the first and second trimester groups were added together to represent those mothers given iodine early in pregnancy for comparison with those first supplemented late in pregnancy (third trimester) or at age 2 (comparison children).

Study children were seen in government buildings in their villages; each child was accompanied by a parent, older sibling, or other family member. Test procedures were performed by Uighur and Chinese physicians and health workers, an American neurologist, a Chinese ear, nose and throat physician, a Chinese psychologist, an American psychologist, and trained volunteers.

Height and head growth were measured and coded as standard deviations from the means on sex and age-specific US growth charts (Hamill et al. 1979). A clinical neurological examination was performed to identify abnormalities of muscle tone and movement. The child performed a 20-meter timed running trial as part of the neurological examination to screen for difficulties with gait and/or coordination. Hearing screening using pure tone audiometry was carried out on all children seen in 1996; a 25-decibel loss in either ear was coded as a meaningful hearing loss.

There are no existing tests of intellectual function standardized for the rural Uighur population. Therefore, the children were tested using several strategies chosen for their previous use in China, use in other developing countries, and/or by virtue of being as non-verbal and non-culture specific as possible (Table II).

The two primary tests of psychological development were the Raven Progressive Matrices (Raven 1960) and the Developmental Test of Visual Motor Integration (VMI; Beery 1989 edition). These tests were chosen to assess learning aptitude in both cognitive (logical thinking and concept development with no motor requirements) and perceptual motor (visual motor abilities) areas. For the Raven test, Chinese normative values for rural children were used (Wang 1989). For both tests, a standard score with a test mean of 100 was derived.

The Purdue Pegboard Test (Tiffin 1987) was used as an additional assessment of fine motor planning and speed; the variables analyzed included raw scores for the number of pegs placed with the dominant hand, the number placed with the non-dominant hand, and the number of successful assemblies of three pieces. Children were screened for significant language delays using the ceiling (5- and 6-year age level) language items from the Denver Developmental Screening Test (DDST; Frankenburg et al. 1975), with items adapted for cultural relevance, translated into Uighur, and administered by an Uighur physician. Language screening resulted in a delay versus no-delay designation.

STATISTICAL ANALYSIS

Statistical analyses were conducted to examine the association between the timing of the first iodine supplement and measures of child growth and development at school age. Group differences on measures with standard scores were assessed using parametric tests, specifically general linear models. Measures resulting in ratio data that were not standard scores (e.g. running times, raw scores on the Purdue Pegboard Test) were tested for group differences using analysis of covariance, controlling for child age. When appropriate, analysis of the relative prevalence of significant impairment in developmental domains was assessed by non-parametric methods (e.g. χ^2 tests) to test the likelihood of significant impairment given the timing of initial iodine supplement. Comparisons between scores from some measures of psychological development were made to examine their psychometric correlations. All statistical analyses were carried out using Statistical Analytic Systems software.

Results

Height and head circumference were assessed in 1996 and coded as standard deviations from US normative values for group comparisons. Results are presented in Table III. There were no statistically significant differences in height related to the timing of iodine supplements given during pregnancy and early childhood.

Head circumference, used as an index of brain growth, was associated with the timing of iodine supplementation. There were statistically significant differences between those supplemented early in pregnancy and those given iodine at 2 years (p=0.05). There was a trend toward statistical significance when comparing those children supplemented in the first or second trimester (early pregnancy) with those whose mothers were given iodine later in pregnancy (p=0.10). In all participants, those receiving iodine earlier had a larger head circumference than those supplemented later.

Table II: Measures used for assessment of psychological development

Domain	*Measure*	*Variable used for analyses*
Perceptual–motor organization	Test of Visual Motor Integration	Mental age (from US norms)/ CA × 100 for standard score
	Purdue Pegboard	Raw scores, controlling for age
Gross motor	Running time 20 m	Time(s), controlling for age
Concept development, logical thinking	Raven Test of Progressive Matrices	Standard score; Chinese normative values for rural children
Language	Denver Developmental Screening Test, language items only, 5- and 6-year items adapted for use with Uighur children, translated to Uighur	Failure at age 6 ceiling items coded as language delay

Hearing was assessed in 186 children in 1996. The percentages of hearing loss, defined as a 25-decibel loss or greater in either ear, ranged from 3.6% for children who received iodine in the first trimester to 7.5% for the comparison group. Group differences were not statistically significant. Four children had a greater than 50-decibel loss in either ear: one whose mother was supplemented in early (1st or 2nd trimester) pregnancy, two during the 3rd trimester, and one from in the 2-year-old comparison group.

Very few children showed neurological symptoms consistent with iodine deficiency disease; and no firm diagnoses of CSH were made in the children seen in either 1996 or 1998. One child seen in 1996 was poorly grown(<–3 SD for weight, height, and head circumference) and developmentally delayed. He had no specific neurological findings, but it could be argued that his development had some components of congenital hypothyroidism. This child received his first iodine supplement during the first trimester of gestation. Otherwise, abnormalities of muscle tone, increased reflexes, and/or gross motor dysfunction were recorded for a total of 15 children: eight received iodine during the third trimester (8% of those seen in the 3rd trimester group), and seven were supplemented during early pregnancy (8.7%). There were no differences in proportions of neurological signs according to group. The children's 20-meter running times were highly associated with chronological age (Pearson's product–moment correlation =–0.58; $p<0.0001$). With age used as a covariate for the test of group differences, no statistically significant differences were associated with the timing of iodine supplementation.

The two primary indices of psychological development were the Raven test and the VMI. The standard scores from these tests met the assumptions for applying parametric tests to group differences. Results are presented in Table IV.

The Raven test was given to the comparison group children in 1996, when these children were approximately 7 years of age. Children supplemented during pregnancy were tested in 1998, when they were old enough to understand test procedures (6 and 7 years). There was a trend toward a statistically significant difference in test scores between those supplemented during pregnancy and those who received iodine during their second year (mean scores 74.5 versus 71.2; $p=0.06$). Otherwise, there were no significant test score differences among the groups. Non-parametric analyses of significant impairment, defined as a standard score of less than 70, were performed. Forty per cent of the comparison group scored in the impaired range compared with 31% of those given an iodine supplement early in pregnancy and 28% of those given supplements during the third trimester (*ns*).

Scores from the VMI, administered in 1996, indicate that young school-age children whose mothers received iodine early in pregnancy had higher scores than those whose mothers were supplemented later in pregnancy (group means 86.2 versus 81.5; $p=0.02$) or first supplemented at 2 years (group mean 72.1; $p=0.0001$; overall $F=30.6$; $p=0.0001$). Of children with a standard score less than 70, 18.8% were supplemented during the third trimester, 75% had been first supplemented after birth up to 2 years of age, and only 6.25% had received iodine supplementation early in pregnancy ($\chi^2=35.8$; $p=0.0001$).

A smaller group of children ($n=85$) were tested on the VMI both in 1996 and 1998, resulting in a correlation of 0.53 (Pearson's product–moment correlation; $p=0.0001$). Also, a group of children, whose mothers were given iodine during pregnancy, were tested on both the VMI and the Raven in 1998 to test convergent validity, resulting in a correlation of 0.42 (Pearson's product–moment correlation; $p<0.001$).

Two-hundred and four children were tested with the Purdue Pegboard Test. Relations between the three scores derived from the Purdue Pegboard Test (dominant hand,

Table III: Height and head circumferences in SD (US normative values; mean, SD)

Timing of initial iodine	*Height*[a]	*Head circumference*[b]
First trimester	–2.13 (0.93)	–0.94 (0.74)
Second trimester	–2.21 (1.0)	–0.41 (0.77)
Early pregnancy	–2.16 (0.98)	–0.52 (0.78)
Third trimester	–2.47 (1.38)	–0.81 (0.99)
24–36 mo (Comparison group)	–2.51 (1.18)	–0.90 (0.90)

[a] *ns*; [b] overall $F=2.93$; $p<0.05$; early pregnancy > controls, $p<0.05$; late pregnancy < early pregnancy, trend only, $p<0.10$ in post hoc tests.

Table IV: Group means (SD) and range of scores from primary measures of psychological status

Timing of iodine supplementation	*VMI (1996)*[a]	*Raven (1998, comparison children tested in 1996)*[b]	*VMI significant impairment, % (SS<70)*[c]	*Raven significant impairment, % (SS<70)*[d]
1st trimester	84.8 (7.6) 72–102	71.9 (10.7) 60–99		
2nd trimester	86.2 (12.04) 62–118	75.8 (12.2) 54–122		
Early pregnancy	86.2 (11.1) 62–118	74.7 (11.6) 53–122	6.3	31
3rd trimester	81.5 (8.8) 61–100	74.5 (11.0) 53–112	18.8	28
2-year-old comparisons	72.1 (11.2) 49–112	71.2 (12.4) 45–109	75	40

[a] Overall $F=30.6$, $p=0.0001$; all between group differences range from $p<0.02$ to $p<0.0001$. [b] Overall $F=1.47$, *ns*; post hoc tests comparisons < early pregnancy supplementation, $p=0.06$. [c] $\chi^2= 36.2$; $p= 0.001$. [d] *ns*.

non-dominant hand, and assembly) ranged from 0.40 to 0.60 (Pearson's product–moment correlations, all $p<0.001$). Controlling for child age, results indicated a significant and positive effect of iodine supplements in early pregnancy (versus 3rd trimester) on performance for non-dominant hand and for assembly ($F=3.20$; $p=0.04$; $F=5.85$, $p=0.006$, respectively) with a trend toward significance for the dominant hand ($F=2.95$, $p=0.06$). The relation between the Purdue Pegboard scores and either the VMI or Raven standard scores was not statistically significant, although there was a trend toward a significance between the score for using the non-dominant hand on the Purdue Pegboard and the standard score on the VMI ($p=0.06$).

The screening for expressive language delays, using 5- and 6-year-level language items from the DDST, resulted in a trend toward finding more delays in children in the comparison group (those given iodine in their second year; $\chi^2=6.78$; $p=0.8$) than those supplemented during pregnancy. The percentage of language delays were: 3.6 for early pregnancy, 4 for late pregnancy, and 20.9 for the comparison group. There was no increase in language delays for the early versus late pregnancy groups.

Discussion

The findings of improved psychological development in school-age children whose mothers were given iodine supplements during early pregnancy (before the end of the second trimester) relative to those supplemented later in pregnancy or in early childhood are consistent with our study of these children as infants (Cao et al. 1994b, DeLong et al. 1998). There were no differences in height at school age between those grouped according to age at initial iodine supplement; but head circumference was significantly larger for those who received supplements during pregnancy and, in particular, for those who were exposed to maternal iodine supplements during the first or second trimester.

There were no diagnoses of CSH in the follow-up studies. The neurological assessments indicated that very few school-age children showed abnormalities in reflexes, muscle tone, or gross motor function consistent with CSH. Other investigators have demonstrated the prevention of congenital hypothyroidism by oral iodine given during pregnancy (e.g. Pharoah and Connolly 1987). In the Pharoah and Connolly study, three individuals with manifestations of CSH from the group of mothers given iodine during pregnancy received iodine at 30, 32, and 34 weeks' gestation (late pregnancy). Their findings may be consistent with those reported here regarding the benefits of iodine supplements in early (1st or 2nd trimester) versus late (3rd trimester) pregnancy.

Although our findings support the importance for the child of an adequate supply of iodine early in pregnancy, they are not consistent across domains of psychological development. The two measures of perceptual motor abilities (VMI and Purdue Pegboard Test) offer convincing support for an association between early iodine in pregnancy and improved visual perception and fine motor abilities at school age. The VMI is a design-copying task found in previous research to be predictive of school readiness tests in Kindergarten (in the United States) and early reading achievement (Beery 1989). The Purdue Pegboard Test adds the demand for speed in a fine motor activity. These test results were consistent with previous studies that reported higher scores on perceptual motor tasks in individuals from iodine-replete versus iodine-deficient populations (e.g. Bleichrodt et al. 1980).

The Raven Progressive Matrices test has been used successfully in other studies of iodine deficiency and results have demonstrated the psychological advantage of an iodine-sufficient environment (Ma et al. 1989). However, other studies that used the Raven test were with older children and adults. It may be that the children tested here (although within the test's age normative values) were too early in their formal education and not experienced with this type of logical thinking task. It may also be that mild learning deficits associated with iodine deficiency are evident in perceptual motor skills in the young child before they show in logical thinking and problem solving later in childhood.

Scores from the measure used to screen the children for language delays did not reflect differences related to the timing of iodine supplements. The DDST is a screening test and only the language items from the DDST were used. The modifications of DDST items to be used in southern Xinjiang resulted in the least standard test in the study. It may be that this method for assessing language was not sensitive enough to detect language delays. Neither the Raven test, a non-motor test of logical thinking and concept development, nor the language screening resulted in statistically significant differences related to the timing of initial iodine supplement, although there were trends toward the same relations as found for the VMI and Purdue Pegboard Test.

The findings concerning psychological, particularly perceptual motor, abilities associated with the timing of initial iodine supplements in this study raise other questions, including whether iodine sufficiency versus insufficiency would be associated with an increase or decrease in achievement at school. If children are more successful in school, are they more likely to stay in school longer? If so, what are the consequences of more formal education for child, family, and community? Correa (1980) used data from the Fierro-Benitez study in Ecuador (1969) to demonstrate that as the prevalence of iodine deficiency decreases, the per capita income increases. In the community he studied, a 7-point increase in IQ was associated with a 10% increase in income.

This research also has important implications for the development of children in industrialized countries as well as for those in developing countries. First, iodine deficiency is not limited to developing countries only; maternal iodine supplementation is being considered in both Europe (Glinoer et al. 1997) and in the USA (Utiger 1999). Second, maternal thyroid deficiency during pregnancy is associated with poorer child outcomes (e.g. Haddow et al. 1999). In the latter study, the children of a group of women identified later as thyroid deficient and not treated during pregnancy had IQ scores on average 7 points lower than those who were treated. Untreated women with thyroid deficiency were four times more likely to have children with an IQ significantly below average (–1SD). Third, studies of thyroxine supplementation of hypothyroxinemic preterm infants have demonstrated a significant increase in IQ at age 2 years in infants treated before the end of the second trimester (27 weeks' gestational age) but not later (van Wassenaer 1997). It is clear from these converging studies with different populations that adequate iodine and thyroid hormone is essential for optimal brain development and that there is a critical period for the effect of thyroxine on brain development at the end of the second trimester of pregnancy.

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