The Hypothyroxinaemia of Prematurity

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Abstract

Transient hypothyroxinaemia of prematurity (THOP) is common. The preponderance of evidence indicates that at the very least THOP is a marker of elevated risk of neurodevelopmental adversity. Existing observational and experimental studies could neither support nor dispute the use of thyroid hormones in preterm infants. The experimental studies done so far had major limitations because of the small number of infants enrolled in the trials. For future large multicenter randomized trials, energies should be focused on assessing neurodevelopment objectively in survivors and consider enrolling only those infants most likely to benefit from thyroid hormones replacement therapy. Moreover, the addition of triiodothyronine (T3) to the treatment schedule needs to be seriously considered.

Key words

Hypothyroidism; Hypothyroxinaemia; Prematurity

Introduction

Hong Kong is one of the few places in the world where cord blood serum thyrotropin level is used for screening of congenital hypothyroidism. Between 26 March 1984 and 30 June 1995, 451,390 newborns were screened for congenital hypothyroidism. One hundred and forty-five babies were diagnosed to have congenital hypothyroidism, the incidence was thus one in 3,113 live-births. Ninety-nine out of 104 babies born between 26 March 1984 to 30 June 1992 were reassessed at the age of three years. Twenty-three cases were proven to have transient hypothyroidism, represented 22% of all cases of congenital hypothyroidism. This high figure may be attributed to the low cut off point for thyroid stimulating hormone (TSH) level in Hong Kong. However, the low iodine levels in salt and water of Hong Kong may also be related. In one local pilot study, 35.8% of the studied healthy pregnant women were found to be iodine deficient by WHO standard. The preterm and low birthweight infants (LBW) are particularly susceptible to transient hypothyroidism. This review article serves to increase our awareness of such phenomena in premature babies.

Low thyroxine concentrations are very common in the first weeks of life in preterm and low birthweight infants. As early as 1977, controlled trial involving 8,831 term and 215 premature infants had been conducted in America to evaluate the prevalence and significance of transient postnatal hypothyroxinaemia on developmental outcome at 12 months of age. The thyroxine values are inversely related to gestational age and birth weight. Such transient hypothyroxinaemia is viewed by many as an adaptive process and does not require treatment. Earlier and smaller studies found no difference in cognitive or developmental measures in these premature infants who had transient hypothyroxinemia. However, its significance for later developmental outcome was then established by observational studies conducted in 1980's in Cambridge, Netherlands and New Jersey.
The Hypothyroxaemia of Prematurity

The premature infant delivered into the extrauterine environment experiences similar thyroid system adaptation changes as occur in term infants. These transitional changes, however, are superimposed on an immature hypothalamic-pituitary-thyroid axis. Relative to term infants at birth, in preterm infants:
- serum thyroxine binding globulin (TBG) and total thyroxine (T4) concentrations are lower,
- tissue type 1 monodeiodinase (MDI) activities – the MDI responsible for most of triiodothyronine (T3) in serum – is lower,
- Thyrotropin – releasing hormone (TRH), serum T3 level and free T4 concentration are lower,
- bioinactive thyroid hormone analogue levels – reverse T3 (rT3) and 3,3-diiodothyronine (T2) – are higher,
- brown adipose tissue thermogenic mechanisms are immature,
- and tissue thyroid hormone response systems are variably immature.

This gestation age – related hypothyroxaemia is referred to as the hypothyroxaemia of prematurity. As indicated, it is characteristic of smaller low birth weight (LBW) infants (30 to 35 weeks gestation age) and all very low birth weight (VLBW) infants.

The Spectrum of Thyroid Function Disorders in Hypothyroxaemic Premature Infants

Hypothyroxaemia usually is defined relative to term infants whose total T4 range has been characterized in regional newborn thyroid screening programs. Values below two standard deviations of the term population are considered low.

Physiologic hypothyroxaemia implies that the low free T4 concentration is "characteristic of or promoting normal or healthy functioning". Whether the hypothyroxaemia of most premature infants (in the absence of elevated serum TSH concentrations, hypothalamic – pituitary disease, or nonthyroidal illness) is physiologic in the sense of promoting normal functioning and development has been controversial. The characterization of LBW premature infant hypothyroxaemia as physiologic has reflected its invariability and our inability to demonstrate clearly that supplemental T4 therapy is necessary, beneficial or harmful, particularly with regard to brain maturation.

Transient primary hypothyroidism is a temporary iodine deficiency in premature infants characterized by low serum T4 and free T4 levels and high thyrotropin (TSH) concentration. This occurs during the first two to three postnatal weeks and is more frequent in VLBW infants in areas of lower iodine intake. The incidence was observed to be inversely proportional to gestational age, indicating that most VLBW infants are capable of increasing serum TSH in response to physiologically significant hypothyroxaemia. Yet, the threshold – free T4 value to stimulate TSH secretion in VLBW infants is not clear. Cord blood T4 and TSH levels are normal in these infants. Urinary iodine excretion and thyroid iodine content are reduced, suggesting that the acquired primary hypothyroid state is the result of limited iodine substrate relative to the increased thyroid hormone needs of early infancy. Iodine treatment will correct the hypothyroxaemia and iodine originating from deiodination of the T4 dose could contribute to the supply. Indeed, it would release 6.5 ug iodine per day for a preterm neonate weighing 1 kg, an amount clearly higher than the iodide intake of very immature neonates.

The transient reduction in total and free T4 concentrations in VLBW infants during the first one to two weeks has been referred to as the transient hypothyroxaemia of prematurity. The effect of extreme prematurity on postnatal maturation of thyroid function was first reported in 1987. The result of this study suggested that there is increasing delay in maturation of the hypothalamic-pituitary-thyroid control system with increasing prematurity over the 23 to 28 weeks range. The relatively low T4 and free thyroxine index (an index indicating level of unbound T4) without elevated serum TSH levels are characteristic of hypothalamic – pituitary or secondary – tertiary hypothyroidism. The normal TSH responsiveness to thyrotropin releasing hormone previously reported in preterm infants at a time when free T4 levels are low suggests that there is an altered set point, relative to term infants, for T4 (and/or T3) feedback control. Recent studies documenting transient, marked reductions in free T4 concentrations in VLBW infants to values below 0.5 to 0.7 ng/dL by immunoassay and without elevated TSH concentrations (>20 U/L) are consistent with the above hypothesis.

The prevalence of permanent congenital primary and hypothalamic – pituitary hypothyroidism is similar in premature and full-term infants. The former is 1 in 4000 and the latter is 1 in 25,000 to 29,000. These values were obtained from screening programs in America and Europe.
The syndrome of *nonthyroidal illness* (NTI), (low T3 syndrome, euthyroid sick syndrome) usually is associated with a decreased caloric intake, a catabolic state, or malnutrition. A state of NTI often is superimposed on the transient hypothyroxinaemia of premature infants. Premature infants have an increased susceptibility to neonatal morbidity, complicated with feeding disorders and relative malnutrition. These factors tend to inhibit T4 to T3 conversion in the neonatal period and further aggravate the extent of the low T3 state characteristic of the early neonatal period in such infants. Levels of T4 and free T4 have been variable in infants with NTI. Increased free T4 concentration has been observed in infants with severe illness, associated with markedly reduced mean T4 and TBG concentrations. The reduced hepatic TBG production and inhibition of T4 binding to TBG tend to increase free T4 levels. In those with mild disease, levels of T4 and free T4 are similar to control infants. The extent of these changes is directly correlated to the severity of illness. Hypoxia and tissue factors, including cytokines, may play a role in the hypothyroxinaemia of NTI.

**Does Transient Hypothyroxinaemia of Prematurity Warrant Treatment?**

**A. Biological Evidence**

**Evidence against Treatment**

All premature infants have some degree of hypothyroxinaemia. A recent large study (n=919) showed that mean thyroxine levels at screening declined from 7.8 ug/dL at 28 weeks of gestation to 5.1 ug/dL at 23 weeks. The New England Regional screening program sets 5.5 ug/dL as the lower threshold for normal thyroxine, meaning that the average infant at 23 weeks will have an abnormal thyroid screen. In 1977, a large prevalence study revealed that up to 50% of infants delivered before 30 week's gestation had hypothyroxinaemia (serum T4 <6.5 ug/dL) and low free T4 values. However, the free T4 levels are not so low as in neonates with congenital primary hypothyroidism; rather they are similar to values in normal adults. There is evidence that the distribution of iodothyronine metabolites in utero is tilted towards the less active forms. For preterm infants, they also seem not to produce T3 from T4 in the first weeks of life, and T3/T4 ratios are lower in preterm than in term infants. Although these observations reinforce the view that the fetus or neonate ordinarily experiences lower levels of active thyroid hormones than do children or adults, it may be that thyroid activity in the brain differs from that measured in the serum. The Madrid investigative team led by Professor Gabriella Morreale de Escobar has demonstrated in a series of publications that thyroid hormones are present in the fetal rat brain at 50% of adult levels in spite of low fetal plasma T3 levels. Moreover, brain 5' deiodinase activity with preference for T4 as substrate, is responsive to hypothyroidism in rat fetal life. Possibly such mechanisms exist in humans during fetal life as well.

**Evidence for Treatment**

The concept that a brief period of thyroid deficiency might adversely affect neurodevelopment is supported by considerable biological information. Children who have endemic cretinism exhibit disabilities that are similar to those associated with prematurity. Both conditions are particularly associated with the form of cerebral palsy (CP) known as spastic diplegia. Sensorineural hearing loss is another condition found in both populations. Boyages and Halpern have argued that the neurologic component of endemic cretinism is attributable to prenatal hypo-thyroidism, with the damage occurring mostly in the second trimester. Premature infants who experience transient hypothyroxinaemia of prematurity (THOP), especially those born at the end of the second trimester, resemble, in both timing of insult and clinical manifestations, infants who have the pure neurologic type of endemic cretinism. Premature infants who have CP experience substantial delays in myelination. The specific role of thyroid hormone seems to be to coordinate the timing of oligodendrocyte differentiation. Barres et al's study showed that oligodendrocytes in cell culture did not differentiate from precursors in the absence of either T3 or T4. This same study also showed that hyperthyroidism can greatly accelerate the appearance of oligodendrocytes in developing rat optic nerve. Thus thyroid hormones may act as timing signals for important processes in neurodevelopment, especially white-matter development, and abnormalities may result from either acceleration or retardation of these processes.

One recent study (n=1414) found that infants with hypothyroxinaemia of prematurity had twice the risk of developing echolucency in their cranial ultrasound scan as their peers with higher thyroxine levels. These findings support the hypothesis that a "normal" blood thyroxine level...
protests infants born near the end of the middle trimester against the risk of cerebral white matter damage.35

B. Observational Studies of Neurodevelopment after Transient Hypothyroxinaemia

Evidence against Treatment

Small studies found no deficits in cognitive or developmental measures in the hypothyroxinaemic premature babies when they grew up.4-6 A recent retrospective case-control study of very low birth weight (VLBW) neurologically impaired infants done by Costello compared the antenatal, intrapartum, neonatal events and therapies of 72 singleton inborn VLBW children born between 1983 to 1991 who had neurologic impairment at 20 months corrected age with 72 neurologically normal VLBW children matched by birth weight, gestational age, race, and sex.36 Multivariate analysis controlling for birth weight, gestational age, race, sex and the birth period (before 1990 versus 1990 and after) could not reveal direct and independent effects of THOP on total neurological impairment.

Evidence for Treatment

The first large study to report an association between thyroid levels at birth and subsequent neurodevelopment was based on an assessment of 18-month old children enrolled at birth in a randomized trial of a nutritional intervention in infants <1850 g cared for in five English neonatal units.37 All subjects had plasma T3 levels obtained twice in the first week and weekly thereafter. Among the 89% of survivors tested, infants whose lowest T3 was below 0.3 nmol/L scored 8.3 points lower on the Bayley mental developmental index and 7.4 points lower on the Bayley psychomotor index than infants with T3 levels >0.6 nmol/L (both P < 0.05). Infants whose lowest T3 levels were between 0.3 and 0.6 nmol/L, had no developmental disadvantage. Mortality to 18 months was almost four times higher (23% versus 6%) in the low T3 group, but growth and cerebral palsy risk were both reported to be unaffected. In 1996, the authors reported on the same cohort of survivors at age 7.5 to 8 years, 236 children (94% of survivors) were examined.7 Based on testing with the abbreviated Wechsler Intelligence Scale for Children (WISC), overall intelligence quotient (IQ) was 6.6 points lower (P<0.05), verbal IQ 8.5 points lower (P<0.05), and performance IQ 5.0 points lower (P=0.01, NS) in children whose T3 had been <0.3 nmol/L, even after adjustment for birth weight, gestation, sex and Apgar scores at five minutes.7

The second study to report an association between THOP and development was based on the follow-up at age two years.8 The Project on Preterm and Small for Gestation Age Infants in The Netherlands was a collaborative survey collecting data on 1338 infants, liveborn in 1983 with a gestational age of less than 32 weeks and/or a birth weight of less than 1500 g. Of the 1338 infants enrolled at birth, 944 survivors were examined at the corrected age of two years. Out of 944 children assessed at the corrected age of two years, screening values between days 5 and 17 could be obtained and linked to the follow up data in 563 cases. The outcome of interest was failure of any one of three directly observed psychomotor tasks – building a tower of three blocks, walking without support, and putting a ball in box upon request. Each of these milestones is reached at the age of 24 months by 90% of a group of normal children. Among children who had T4 levels one standard deviation (SD) below the national screening program mean, 6.8% failed one of these tests. Among children 1 to 2 SD's below the mean, 11.0% failed; among children 2 to 3 SD's below the mean, 17.6% failed. Children more than 3 SD's below the mean (30% of the study population) failed 20.2% of the time. When the 13 potential confounding factors were included in the multivariate regression, this stepwise increase in risk of failure was not altered, and by use of the regression model it was estimated that with each SD drop in T4 in the range studied, the risk of test failure increased by 40% (95% confidence intervals 10% to 90%).

This study too had produced a report describing findings in school-age children. In this analysis, more surviving children were included than in the earlier report, apparently because more linkages had been made between study records and the national screening program since the age two report.38 At the age of 5, 96% of survivors (n=640) were available for examination. They were examined by one of three specially trained paediatricians who administered the Touwen neurologic examination, the Denver Developmental Screening Test (DDST), and a Dutch speech and language scale. Eighty-five (13.3%) had a disability and ninety-two (14.3%) were handicapped following World Health Organization (WHO) usage. At the age of 9, parents of the 83% of survivors (n=552) answered a questionnaire on school performance. Three hundred (54.3%) were in mainstream education in a grade appropriate for age, 151 (27%) were in mainstream education with grade retention, and 101 (18.3%) were in special education. Neurologic dysfunction at age 5 years and school failure at age 9 years were significantly related to lower neonatal thyroxine levels even after adjustment
Evidence for Treatment

Earlier study had suggested that thyroid hormone administration decreased mortality in neonates with respiratory distress syndrome, but this had not been confirmed and developmental follow up was not available.39

Evidence against Treatment

Chowdhry et al studied the effect of thyroxine treatment in 23 infants with gestational age ranging from 26 to 28 weeks, each of whom had serum T4 values less than 4 ug/dL (50 nmol/L) on two occasions and serum TSH values less than 20 mU/L.40 The infants were treated with 10 ug/kg per day of Na-1-thyroxine or placebo. Therapy was given intramuscularly for one to two weeks and then orally. If there was no increase in serum T4 within one week, the dose of T4 was increased to 15 ug/kg per day. Mean birth weight in the control and treated infants approximated 800 g; the increments in weight gain, head circumference, and length were identical over a treatment period of 10 weeks in the two groups of infants. Developmental data revealed no significant difference in the mental, motor, or gross neurologic outcome in the treated and non-treated infants after one year of follow up.

A recent small-sized, randomized, controlled trial (RCT) assessed the endocrine and clinical effects of increasing serum T4 levels in preterm newborns with a gestational age <31 weeks.41 Forty newborns were randomized in a double blind protocol: 20 infants received a daily dose of 20 ug/kg L-T4 for two weeks, whereas 20 control infants received saline. Three newborns in each subgroup died within the first weeks, leaving behind 17 subjects in each arm. Neonatal illness and outcome was evaluated by noting heart rate, oxygen requirement, duration of ventilation, development of chronic lung disease, oral fluid intake, and weight gain; a Bayley score was done at the corrected age of seven months. None of the differences in the increments in weight gain, head circumference, and length were significant. Developmentaldata revealed no significant difference in the mental, motor, or gross neurologic outcome in the treated and non-treated infants after one year of follow up.

C. Experimental Studies of Neurodevelopment after Treatment with Thyroxine

Evidence for Treatment

In 1966, Reuss et al reported on the findings of the Central New Jersey Neonatal Brain Hemorrhage Study (NBH), a regional cohort of 1105 newborns weighing 2000 g or less in three New Jersey (NJ) counties.9 Serum T4 levels were obtained from the NJ State screening program and were classified, as in the Dutch studies, by SD’s below the norms. After adjustment for several potentially confounding variables, T4 levels >2.6 SD’s below the state-set mean were not associated with a 1.3-fold increase in risk.

Evidence against Treatment

In 1993, all infants were treated without regard to baseline

Later, the first moderate-sized, RCT of T4 administration appeared in the literature. Van Wasenaer and colleagues administered 8 ug/kg of thyroxine or placebo daily from 12 to 24 hours after birth for six weeks to 200 infants born at 25 to 30 weeks’ gestation in the Academic Medical Center of the University of Amsterdam in 1991 to 1993.42 All infants were treated without regard to baseline
thyroid status. Double blindness was maintained throughout the study. Thyroxine treatment completely abolished the decline in T4 seen in the control group, and plasma-free T4 was significantly higher in treated infants in all seven measurements performed between days 3 and 42. Thyroxine administration had no effect on the risk of oxygen supplementation at 36 weeks or on major neonatal brain lesions but was associated with seven more cases of lower-grade cerebral hemorrhage, eight fewer cases of patent ductus arteriosus, and seven fewer deaths (all contrasts not statistically significant).

Neurodevelopmental assessment were made at 6, 12, and 24 months. No significant placebo-treatment differences in Bayley mental or psychomotor scores were found in any of the assessments. No significant differences were found in neurologic assessments, but the differences tended to favor the treated group. The placebo group had nine children with neurologic abnormalities at each of the three assessments, whereas the treatment group had five or six. One interesting finding is that in thyroxine-treated infants born at gestational ages of less than 27 weeks, the score on Bayley Mental Development Index at 24 months of age was 18 points higher than the score for the infants with similar gestational ages at birth in the placebo group (P=0.01). However, for thyroxine-treated infants born at 27 weeks or later, the mental-development score was 10 points lower than that of their counterparts in the placebo group (P=0.03). Overall, the authors concluded that supplementation did not improve developmental outcomes.

Apart from neurodevelopmental outcome, Van Wassenaer also studied the somatosensory evoked potentials and motor nerve conduction velocity in relation to L-thyroxine supplementation. The conclusion was that neither the cortical N1 peak latency nor motor nerve conduction velocity improved as a result of the L-thyroxine supplementation during the first six weeks of life in infants <30 weeks' gestational age.

A review done by the Cochrane Neonatal Group was first published in 1999. This review did not support the use of thyroid hormones in preterm infants to reduce neonatal mortality, improve neurodevelopmental outcome or to reduce the severity of respiratory distress syndrome. The small number of infants enrolled in the trials limited the power of the meta-analysis to detect a moderate, but potentially important change in neurodevelopmental outcome. Moreover, a lack of comparability of treatment methods (T3 or T4), dosages, enrollment criteria, developmental test or time of follow-up prevented pooling of the studies for analysis.

D. What Should We Use? T4/T3? and at What Dosage?

The administration of thyroxine to infants of less than 30 weeks' gestation does not increase plasma triiodothyronine (T3) concentrations, which suggest that these preterm infants have not lost their fetal habit. T4 and rT3 were significantly increased in the T4 group. TSH concentrations were depressed in the T4 group and T3 was significantly decreased, probably as a result of TSH depression. The T4/T3 and T4/rT3 ratios differed significantly between the two study groups. This would imply that any treatment to prevent the damage would need to be given in the form of T3. In the management of hypothyroid patients, doctors prescribe thyroxine replacement, and this acts as a pro-hormone for T3. This strategy is unlikely to work in premature babies, and the implication of the work of Lucas and colleagues is to give infants with low T3 concentrations T3 replacement. However, this will not be easy and may be dangerous. Children with thyrotoxicosis do much worse at school than children with hypothyroidism, and some data suggest that intrauterine exposure to high maternal concentrations of thyroxine may have serious long-term consequences.

E. Strategies for a Future Randomized Trial

For future clinical trials, energies should be focused on assessing neurodevelopment objectively in survivors. A new multicenter trial of newborn supplementation with thyroid hormone should be developed that is carefully planned to have sufficient power to assess neurodevelopment in treated and untreated infants under a variety of baseline conditions. To detect the magnitude of effect on the incidence of abnormal neurological outcome as found in the study by Van Wassenaer 1997, a trial would need to enroll 1670 infants. This number would provide 80% power to detect a 40% reduction in death or neurological abnormality (from 12% to 7%) at the 95% confidence level (assuming a 25% mortality rate).

Future trials should also consider enrolling only those infants most likely to benefit from thyroid hormone treatment. This may include enrolling only infants <27 weeks' gestation and using thyroid hormones as treatment in infants with low thyroid hormone levels instead of prophylaxis. In that case a cutoff value (adjusted for gestational age) has to be identified for the plasma free T4 concentration below which thyroid hormone treatment may be beneficial.

As the conversion of T4 to T3 is impaired in premature babies, the addition of T3 to the treatment schedule also needs to be seriously considered. But the dosage and
monitoring schedule have to be further carefully elucidated.

F. Randomized Trials of TRH Administration in Labour

Another approach to the problem of deficient thyroxine in preterm infants has been supplementation of mothers in labor with thyrotropin-releasing factor. Four randomized trials examining end points have been fully published in the literature, and additional trials have been reported in abstract form. All but one of the trials produced lower rates of RDS in the treated group, but the study that failed to do so was the largest and is the only trial thus far to report on later neurodevelopment. This trial has reported (based on questionnaires administered to mothers) that development at approximately age 12 months is slower in some dimensions in the treated group than in control group. Although questions have been raised about the methods of this trial, particularly the reliance on maternal reports of an unstandard nature, the adverse findings described must serve to caution us not to assume that interventions beneficial for newborn functioning necessarily benefit later neurodevelopment.

One major concern of such antenatal thyrotropin-releasing hormone trials is the uncertainty about whether prenatal TRH consistently abolishes THOP. As reported in literature, one TRH Collaborative Trial revealed that the stimulatory and suppressive effects of antenatal TRH treatment observed at birth are transient and do not affect pituitary-thyroid responsiveness at 28 days of age. Thus, we must be cautious in using this approach to evaluate the developmental outcome of treated/untreated THOP.

Conclusion

THOP is a relatively common condition whose long-term effects remain uncertain. The preponderance of evidence indicates that at the very least THOP is a marker of elevated risk of neurodevelopmental adversity. Existing observational and experimental studies could neither support nor dispute the use of thyroid hormones in preterm infants. The experimental studies done so far had major limitations because of the small number of infants enrolled in the trials, with the largest study enrolled only 200 infants. For future large (n>1669) multicenter randomized trials, energies should be focused on assessing neurodevelopment objectively in survivors. Future trials should also consider enrolling only those infants most likely to benefit from thyroid hormones replacement therapy, namely those under 27 weeks' gestation. Moreover, as the conversion of T4 to T3 is impaired in premature babies, the addition of T3 to the treatment schedule needs to be seriously considered. Furthermore, since local pilot study revealed iodine deficiency in 35.8% of the studied healthy pregnant women and the effect of iodine deficiency may probably be more significant in preterms, one will probably choose to treat rather than to withhold treatment.

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