

Hypothyroxinemia is not harmless in preterm infants

Delahunty C, Falconer S, Hume R, Jackson L, Midgley P, Mirfield M, Ogston S, Perra O, Simpson J, Watson J, Willatts P, Williams F. Levels of neonatal thyroid hormone in preterm infants and neurodevelopmental outcome at 5½ years: Millennium Cohort Study. *J Clin Endocrinol Metab* 2010. jc.2010-0743 [pii];10.1210/jc.2010-0743 [doi]

SUMMARY

BACKGROUND

Transient hypothyroxinemia is the most common thyroid dysfunction of premature infants, leading to adverse fetal neurodevelopment. However, the validity of these associations is uncertain because studies have been adjusted for a different range of factors likely to affect neurodevelopment. The aim of this study was to describe the association of transient hypothyroxinemia with neurodevelopment at 5.5 years of corrected age. Although transient hypothyroxinemia was previously thought to be without clinical significance, more recent studies have found adverse associations between transient hypothyroxinemia and neurodevelopment. Transient hypothyroxinemia is characterized by temporary postnatal reductions in whole blood levels of thyroxine (FT₄) with normal levels of thyrotropin (TSH)

STUDY GROUP AND METHODS

The Study Cohort

The children in this study are from a cohort of infants recruited from January 1998 through August 2001, (Millennium study). The infants were born at ≤34 weeks' gestation (n = 666) or at least 37 weeks (n = 135), from November 1999 through August 2001. Term infants were included to validate the McCarthy scales with a Scottish population. The children were assessed at a mean (±SD) of 5 years 6 months (±2 months) (corrected for gestation). The majority of assessments were performed in the child's hospital of birth (47%) or school (27%), but if the children had moved, testing was performed in the child's general practitioner's premises (17%) or at home (8%).

The McCarthy Scales

For this study, the McCarthy scales provided information on fine and gross motor skills and cognitive development. The scales contain 18 tests, grouped into six scales: verbal, perceptual performance, quantitative, general cognitive, memory, and motor function. Each assessment lasted about 90 minutes and was performed by one of three psychologists trained to use the McCarthy scales, and their performance was audited regularly. The population mean is 100 for the general cognitive scale and 50 for the other scales. The child and the person bringing the child in for assessment each completed a British Picture Vocabulary Scales assessment (BPVSI), which provided an indication of their verbal IQ. The person bringing the child also completed a questionnaire recording significant illnesses or events that had occurred between discharge from the neonatal unit and the child's 5.5-year assessment.

Hypothyroxinemia

Transient hypothyroxinemia was defined as a serum thyroxine (T₄) on day 7, 14, or 28 that was no greater than the 10th percentile for cord serum corrected for gestational age. To classify the hypothyroxinemic status of an infant on postnatal day 7 who was

born at 26 weeks' gestation, the cutoff level of T₄ was a value less than or equal to the 10th percentile of cord serum measured in all infants in the Millennium cohort born at 27 weeks' gestation; day 14 levels were compared with 28-week gestation, and day 28 levels were compared with 30-week gestation. This was based on the notion that brain growth follows a predefined pattern, whether in utero or ex utero, in which the T₄ levels in the premature infant should ideally be within the range of T₄ levels of an infant of the equivalent gestational age, while current cord levels are the best proxy for in utero levels. Euthyroid status was defined as a serum T₄ on day 7, 14, or 28 that was greater than the 10th percentile and less than the 90th percentile of cord serum, corrected for gestational age. Transient hyperthyroxinemia was defined as a serum T₄ level on day 7, 14, or 28 that was ≥90th percentile.

Factors Associated with Neurodevelopment

Twenty-six factors identified from the literature that were potentially associated with neurodevelopment, and for which the authors had information collected either during the Millennium study or from the British Association of Perinatal Medicine (BAPM) score that was used as a proxy for severity of illness. The BAPM scoring system was devised to quantify resources required by UK neonatal intensive care units, in which severity of illness is related to the amount of resources required, decreasing from levels 1, 2, and 3 to normal care, with 1 being severe illness.

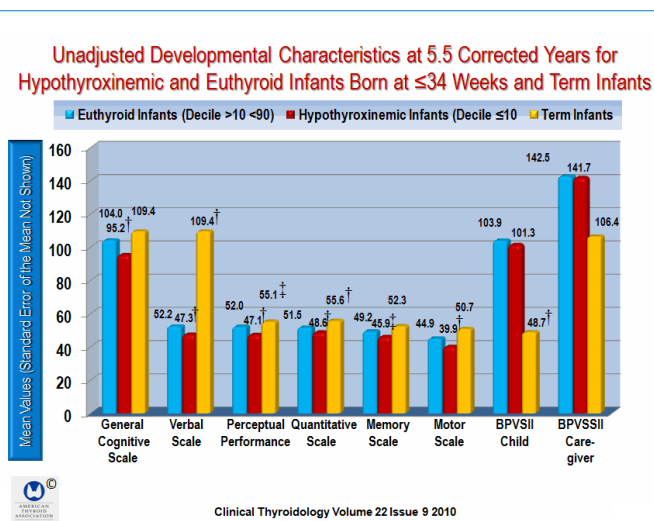


Figure 1. This figure shows the unadjusted developmental characteristics at 5.5 corrected years for infants with hypothyroxinemia and euthyroid infants born at ≤34 weeks' gestation and for term infants. For both the groups of infants, the percentage below 2 SD of the population mean is displayed. The figure shows the significant effect on the general cognitive scale, on the verbal scale, the perceptual performance, quantitative scale, memory scale motor scale, and BPVSI for both the child and the child's caregiver. †P<0.001. ‡P< 0.05. The data in this figure are derived from Table 2 of Delahunty et al.

The 26 potential independent confounding variables for the evaluation of neurodevelopment were maternal characteristics (smoking history, marital status, BPVSII, maternal age, treated maternal thyroid disease), intrapartum outcomes (use of epidural, spinal or general anesthesia; opiates; or Entonox (during labor), sex of the infant, BWR (ratio of the actual birth weight and the mean Scottish birth weight for the appropriate gestational age), multiple births, mode of delivery, gestation, hospital of birth, BAPM score of level 1 or a level 2 to 3 score at day 7 with or without day 24 or day 28, thyrotoxic status, parental lifestyle (maternal postnatal depression or maternal depression), birth order, number of months breast-feeding, attendance at nursery group, fostering of a child, death of close family member, or moving home.

RESULTS

Of the 666 infants recruited at ≤34 weeks' gestation, hypothyroxinemic status could be categorized for 528. The authors assessed 442 infants, 120 (3%) of whom were categorized as hypothyroxinemic; their data were excluded for the present analysis. A total of 100 term infants (≥37 weeks' gestation) were assessed. From the group followed and reported on by the authors, 89 of 442 infants at ≤34 weeks' gestation (20%) were classified as hypothyroxinemic; 31 of 82 at 23 to 27 weeks' gestation (38%), 38 of 166 at 28 to 30 weeks' gestation (23%), and 20 of 194 at 31 to 34 weeks' gestation (10%).

Factors That Identify Children with Hypothyroxinemia

Two factors distinguished the children classified as hypothyroxinemic: a lower gestational age at birth (28 vs. 30 weeks; P<0.0001) and a higher proportion of infants with level 1 BAPM scores on day 7 and day 14 or 28 (56 vs. 14%; P<0.0001). Infants with hypothyroxinemia scored significantly worse than euthyroid infants on all McCarthy scales except for the quantitative subscale.

Adjusting for the Main Confounders of Neurodevelopment

The unadjusted differences were general cognitive scale (9 points), its three subscales (5, 5, and 3 points), memory (3 points), and motor scales (5 points). There was no difference in BPVSII scores of the person bringing the child for assessment. For all tests, a significantly higher proportion of infants with hypothyroxinemia as compared with euthyroid infants scored <2 SD values of the population mean. (Figure 1). After adjustment for the main confounders of neurodevelopment, infants with hypothyroxinemia still scored worse than euthyroid infants on the McCarthy scales, although the magnitude of the difference was attenuated as compared with the unadjusted scores. Infants with hypothyroxinemia scored significantly lower than euthyroid infants on the general cognitive score (7 points) and its verbal subscale (5 points). The adjusted difference for the quantitative (1 point) and perceptual performance (3 points) subscales, motor scale (2 points), and memory scale (3 points) were not significantly lower (Figures 2 and 3).

McCarthy Scales and Subscales versus BAPM Scores

The authors opine that the BAPM scores were the most persistent and detrimental influence on the McCarthy scales. Moreover, the BAPM level 1 infants (the sickest) scored

significantly worse on all scales and subscales, ranging from 12 points lower on the general cognitive scale to 5 points lower on the quantitative subscale (Figure 4). Infants of mothers with treated thyroid disease scored significantly higher than infants with euthyroid mothers on the general cognitive scale (19 points) and its subscale (19 points) and the subscale of perceptual performance (12 points). Small increments were

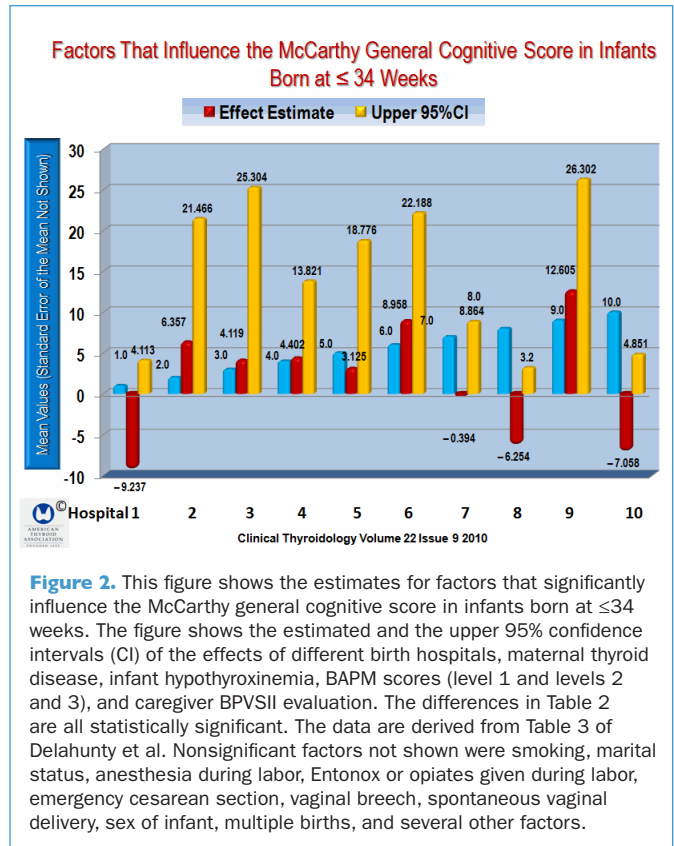


Figure 2. This figure shows the estimates for factors that significantly influence the McCarthy general cognitive score in infants born at ≤34 weeks. The figure shows the estimated and the upper 95% confidence intervals (CI) of the effects of different birth hospitals, maternal thyroid disease, infant hypothyroxinemia, BAPM scores (level 1 and levels 2 and 3), and caregiver BPVSII evaluation. The differences in Table 2 are all statistically significant. The data are derived from Table 3 of Delahunty et al. Nonsignificant factors not shown were smoking, marital status, anesthesia during labor, Entonox or opiates given during labor, emergency cesarean section, vaginal breech, spontaneous vaginal delivery, sex of infant, multiple births, and several other factors.

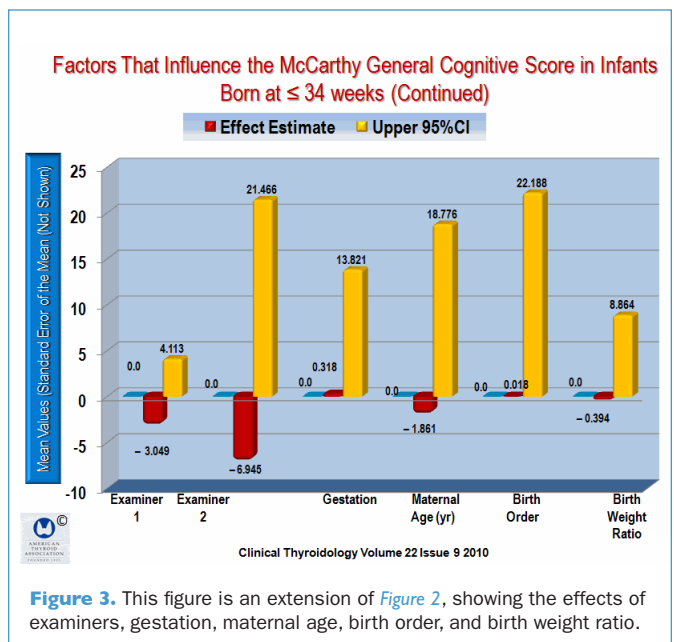


Figure 3. This figure is an extension of Figure 2, showing the effects of examiners, gestation, maternal age, birth order, and birth weight ratio.

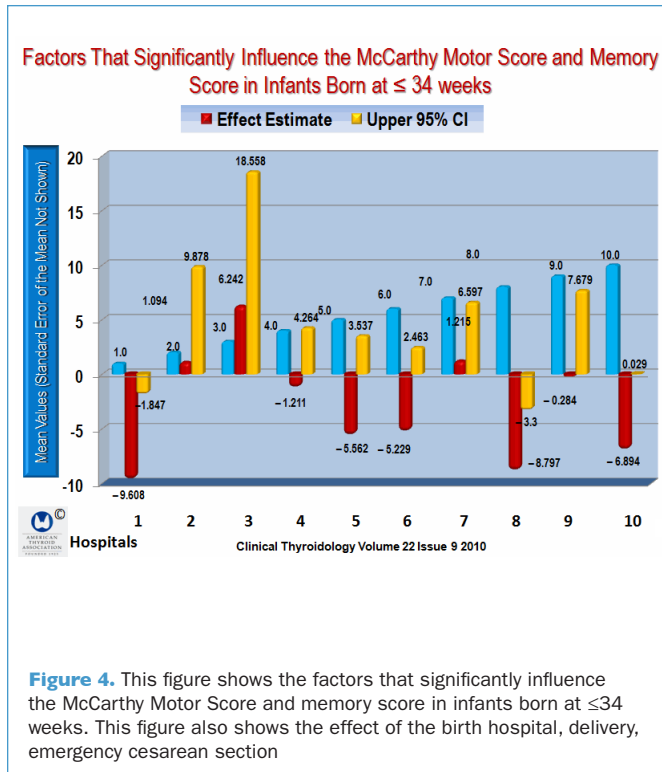


Figure 4. This figure shows the factors that significantly influence the McCarthy Motor Score and memory score in infants born at ≤34 weeks. This figure also shows the effect of the birth hospital, delivery, emergency cesarean section

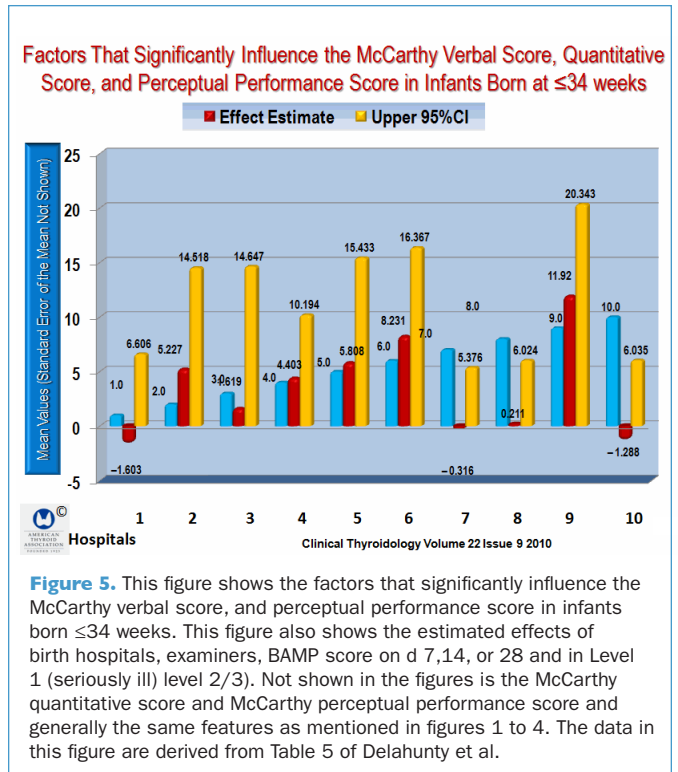


Figure 5. This figure shows the factors that significantly influence the McCarthy verbal score, and perceptual performance score in infants born ≤34 weeks. This figure also shows the estimated effects of birth hospitals, examiners, BAMP score on d 7,14, or 28 and in Level 1 (seriously ill) level 2/3). Not shown in the figures is the McCarthy quantitative score and McCarthy perceptual performance score and generally the same features as mentioned in figures 1 to 4. The data in this figure are derived from Table 5 of Delahunty et al.

found between BPVSII of the person bringing the child for testing and the general cognitive score, its three subscales, and the memory scale. In all, 100 term infants were assessed (Figure 5). The group's mean score on the general cognitive scale was 109, which is significantly higher than the general population norm ($P < 0.001$). The differences in test scores between euthyroid and

term infants were generally less marked than the differences between infants with hypothyroxinemia and euthyroid infants.

CONCLUSION

The findings in this study do not support the notion that the hypothyroxinemic state is harmless in preterm infants.

COMMENTARY

Transient hypothyroxinemia is a common finding in premature infants that has been thought not to have long-term sequelae or to require treatment. Reuss et al.(1) investigated whether hypothyroxinemia in premature infants is a cause of subsequent motor and cognitive abnormalities. In this study, the authors retrieved blood thyroxine values during routine screening in the first week of life in children who weighed ≤2000 g at birth and were born at ≤33 weeks' gestation who were enrolled in a population-based study of the late sequelae of neonatal brain hemorrhage. The effects of severe hypothyroxinemia, defined as a blood thyroxine value >2.6 SD below the mean for New Jersey newborns, were assessed before and after adjustment for gestational age and potentially confounding variables. After adjusting for gestational age and multiple prenatal, perinatal, and early and late neonatal variables, severe hypothyroxinemia was found to be associated with an increased risk of disabling cerebral palsy (odds ratio, 4.4; 95% confidence interval [CI], 1.0 to 18.6) and a reduction of nearly 7 points (95% CI, 0.3 to 13.2) in the mental-development score. The authors concluded that severe hypothyroxinemia in preterm infants may be an important cause of problems in neurologic and mental development detected at the age of 2 years.

In a study by Meijer et al. (2) of 563 preterm children born at <32 weeks' gestation with a very low birth weight (<1500 g), the relationship between neonatal thyroxine concentration and psychomotor development was assessed at 2 years of age. The study found a significant association between low neonatal thyroxine concentration and a negative score on the three milestones of development (three developmental milestones chosen for analysis were obtained by direct observation of the child: builds tower by direct observation [coordination] walks without support [gross motor function], and puts a ball in a box by request [passive language]). The authors concluded that their findings do not support the view that transient hypothyroxinemia in preterm infants is harmless.

More recently, Simic et al. (3) studied 64 infants born at 24 to 35 weeks' gestation who were stratified into four gestational age groups: group A, 23 to 26 weeks (n = 10); group B, 27 to 29 weeks (n = 23); group C, 30 to 32 weeks (n = 20); and group D, 33 to 35 weeks (n = 11). The controls were 33 full-term healthy infants (group E).

Free thyroxine (FT₄), triiodothyronine (T₃) and TSH were measured at 2 and 4 weeks of life and at 40 weeks' postconceptional

age. At 3 months corrected age, all infants were assessed with the Bayley Scales of Infant Development-Second Edition (BSID-II), from which both mental development index (MDI) and psychomotor development index (PDI) scores and four indexes of attention were evaluated: sustained attention, selective attention, attention shift, and total attention. The gestational age-stratified preterm groups differed significantly in T_3 and FT_4 levels at 2 and 4 weeks of life in infants born at <27 weeks' gestation. Preterm infants scored significantly below full-term infants on BSID-II, MDI, and PDI and selective, sustained, and total attention scales. In the preterm group, FT_4 levels were positively associated with PDI and selective, sustained, and total attention. The conclusion was that reduced levels of thyroid hormone in the neonatal period in preterm infants are associated with a reduced neurocognitive outcome in the attention domain at 3 months corrected age.

Lastly, van Wassenaer et al. (4) conducted a randomized, controlled trial with T_4 supplementation in infants born at <30 weeks' gestation and with the last neurodevelopmental follow-up at the age of 5.5 years. T_4 supplementation was associated with an improved outcome of infants born at <28 weeks' gestation and a worse outcome of infants born at 29 weeks' gestation. The authors studied gestational age-dependent effects of T_4 supplementation at the mean age of 10.5 years in children participating in this randomized, controlled trial. Questionnaires regarding school outcome, behavior, quality of life, motor problems, and parental stress were sent to the parents and children and their teachers at the same time point for all surviving children 9 to 12 years of age. A total of 72% of the families responded to the questionnaires. Nonrespondents had more sociodemographic risk factors and worse development until 5.5 years. At the mean age of 10.5 years, T_4 supplementation was associated with a better school outcome in those who were born at <27 weeks' gestation and a better motor outcome in those who were born at <28 weeks' gestation, whereas the reverse was true for those who were born at 29 weeks' gestation. No other gestational age-dependent outcomes were found. The authors concluded that gestation-dependent effects of T_4 supplementation remain stable over time. These effects do not prove beneficial effects of T_4 in infants born at <28 weeks, but the authors suggest that this should be the background for a new randomized, controlled trial with thyroid hormone in this age group.

Delahunty et al. conducted an important study of 442 infants born at ≤ 34 weeks' gestation who had a serum T_4

measurement on postnatal day 7, 14, or 28 that was compared with 100 term infants who had serum T_4 measurements in cord blood and follow-up at 5.5 years. The infants with hypothyroxinemia, defined as a T_4 level ≤ 10 th percentile on day 7, 14, or 28 corrected for gestational stage, had scores that were significantly lower on McCarthy scale testing than those of euthyroid infants with a T_4 level greater than the 10th percentile and less than the 90th percentile on all days on all McCarthy scales except the quantitative scales. After adjusting the McCarthy scales for 26 confounders of neurodevelopment, the scores of infants with hypothyroxinemia were significantly lower than on the general cognitive and verbal scales as compared with euthyroid infants.

This study found that the most persistent and detrimental influence on the McCarthy scales was the BAPM scores. The British Association of Perinatal Medicine (BAPM), founded in 1976, is an association of professionals who have a special interest in the care of fetuses and newborn babies. Using the available evidence, a working group of BAPM, in consultation with the membership, the Royal Colleges, and the Neonatal Nurses Association, prepared the first edition of this document.

Compared with preterm euthyroid infants, the preterm infants with hypothyroxinemia were born earlier and were more often categorized as sicker (BAPM level 1) during the first 28 postnatal days. The authors of this study indicated that the consistent detrimental association between BAPM 1 and all aspects of developmental assessment were anticipated. The authors previously had shown that the BAPM score, while just a management tool to determine the level of nursing support required, is a very good proxy for severity of infant illness.

Delahunty et al. concluded that how the changing demographic pattern affects hypothyroxinemia is not clear, but it is possible that the hypothyroxinemia observed in their cohort is still no more than a consequence of other, as yet unidentified confounders. However, in the context of this analysis, the authors suggest that their findings do not support the view that the transient hypothyroxinemic state in preterm infants is entirely harmless.

This appears to be the consensus of most studies, and it seems reasonably certain that randomized, prospective studies will be necessary to fully understand the pathophysiology of this problem.

— Ernest L. Mazzaferri, MD, MACP

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