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Congenital Hypothyroidism: Optimal Initial Dosage and Time of Initiation of Treatment: A Systematic Review

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Abstract

Context: Appropriate management of neonates, tested positive for congenital hypothyroidism (CH), in particular, the initial dosage of levothyroxine and the time of initiation of treatment is a critical issue. The aim of this study was to assess all current evidence available on the subject to ascertain the optimal initial dose and optimal initiation time of treatment for children with CH.
Evidence Acquisition: In this study, all published research related to the initiation treatment dose and the onset time of treatment in congenital hypothyroidism were reviewed. The searched electronic databases included Medline, Science direct, Scopus EMBASE, PsycINFO, Cochrane, BIOSIS and ISI Web of Knowledge. Additional searches included websites of relevant organizations, reference lists of included studies, and issues of major thyroid and pediatrics journals published within the past 35 years. Studies were included if they were written in English and investigated levothyroxine dose or timing of treatment or both, used for the treatment of children with congenital hypothyroidism.
Results: Two thousand three hundred and seventy-four articles (excluding duplicates) were retrieved from the primary search. After reviewing the titles, abstracts and full-texts of studies, eventually, 22 studies were found that met our inclusion criteria. Amongst these, 17 and 12 evaluated outcomes of different treatment doses and treatment timing, respectively. Overall, the majority of these studies emphasized the initial high dose of levothyroxine and early treatment of newborns with hypothyroidism. There were, however, some studies that disagreed with increasing levothyroxine dose at initiation of treatment.
Conclusions: Considering the results of this review, apparently there is no difference in opinion regarding the early initiation of treatment, whereas determining the optimal dose of levothyroxine for start of treatment in CH patients still remains a controversial issue, demonstrating the need for further studies, despite the fact that use of high doses can lead to rapid normalization of biochemical indices, although this may cause complications.

Keywords: Congenital Hypothyroidism, Starting Treatment Dose, Treatment Initiation Timing, Review Article

1. Context

Congenital hypothyroidism (CH), one of the most prevalent endocrine diseases, is known as a common preventable cause of mental retardation (1). Mass population screening of newborn infants for CH, first introduced in 1974, is today a routine and effective tool of timely/early diagnosis of CH, used throughout the world (2). Detection of children with CH by screening programs and treatment with levothyroxine is currently the standard method for the control of CH, a cause of mental retardation (3). Available data shows that during pregnancy very little thyroxine crosses the placenta from the mother to the fetus and most children are born without signs or symptoms of hypothyroidism (4, 5). Following diagnosis, if tested positive for CH, what is important is the early treatment of children with CH, using an appropriate initiation dose of levothyroxine sodium.

Previous studies, conducted over the past three decades earlier, show that initiation of treatment within the first two to three weeks of life resulted in both normal IQ and physical growth (6, 7). Intellectual outcomes in children with CH are affected by bone age, initial serum T4, hypothyroidism etiology, and age at which treatment is started. Those with bone ages of < 36 weeks' gestation, had the lowest T4, and were a thyroid, and those treated later than four weeks were most vulnerable to mental retardation and physical incomplete growth (8, 9).

From the very beginning of treatment of congenital hypothyroidism with levothyroxine (LT4), initially recommended doses of this medication were in the 5 - 7 μg/kg/day range; subsequently, the recommend dose was changed to 8 - 10 μg/kg/day and, most recently, 10 - 15 μg/kg/day was recommended by the American academy of pediatrics, e.g. a 50 μg tablet for infants with a T4 < 5 μg/dL (60 nmol/L (10, 11). Episodes of overtreatment during the first six months of CH treatment period may be a risk factor for sustained attention and inhibitory control at school age (12). Lower doses of thyroxine, account for poorer outcomes in some children (13), indicating the criticality of proper management of these children.

Available data show that there is an excellent prognosis for infants with CH, if detected early and treated without delay (14); however since determination of the optimal initial treatment dose of Levothyroxine and also specification of time of CH treatment are still considered challenging issues, in this review article, based on reviewing all existing evidence and latest findings of this field, we sought to put together and provide the most relevant, updated information on the optimal initial dose and the precise initiation timing for treatment in children with congenital hypothyroidism. This study aimed at providing more information on controversial issues regarding the optimal initial dosage of levothyroxine and onset time of treatment in children with congenital hypothyroidism.

2. Evidence Acquisition

2.1. Search Strategy

In this review, different combinations of the terms levothyroxine dose, initial levothyroxine dose, initiation levothyroxine dose, congenital hypothyroidism treatment timing, initiation time of congenital hypothyroidism treatment and congenital hypothyroidism therapy were used in Cochrane library, PubMed and Scopus to search for all relevant articles published until 28th of September 2015. In addition, by hand-searching we searched reference lists in review articles, relevant textbooks, relevant websites, and expert reports. Forward citation searches were conducted for all studies that met the inclusion criteria and were published before the mentioned date. Our search was not limited to clinical trials, and all studies that met the inclusion criteria were included in the review. Our eligibility criteria were inclusion of studies related to the treatment of children with congenital hypothyroidism, without considering their gender.

2.2. Study Selection

Two reviewers independently reviewed and scanned the titles and abstracts of all studies generated by the search. For all potentially relevant articles, hard copies were retrieved, and these studies were assessed by the two reviewers independently to determine whether or not they met the inclusion criteria.

All of the studies found in this review, were researches that assessed initial treatment dose or timing (time of initiation of therapy) or both. Hence, we classified the results of studies in two categories, including the initiation time of treatment and initial dose of L-thyroxine for management of congenital hypothyroidism.

2.3. Critical Assessment of Articles

All selected studies were critically evaluated in terms of the probability of bias and confounding effects; for each article included in this systematic review, using the STROBE 2007 (v4) Statement-Checklist (15), risk of biases including probability of selection bias, loss during follow up bias, and confounders were assessed.

2.4. Studies Analysis

After critical appraisal of the studies selected for this review, we extracted the study design and main results for each study and classified its findings, the initial treatment dose and initiation time of treatment, separately. Finally, using the results of these studies to collect evidence, the authors extracted and highlighted/underscored the most critical issues regarding the initiation time and optimal dose of levothyroxine in treatment of children with CH.

3. Results

Two thousand three hundred seventy-four articles (excluding duplicates) were retrieved from the primary search in electronic databases, and another 74 from additional search methods, including hand-searches of textbooks, reports opinions, and the forward citation search. We did not find any randomized controlled trials related to the treatment of CH, and we found only one randomized, double-blind trial that compared a full starting levothyroxine dose of 1.6 μg/kg with a low starting dose of 25 μg (increased every four weeks) in patients (not children) with newly diagnosed cardiac asymptomatic hypothyroidism (16). Fifty-three potentially relevant studies were evaluated against the inclusion criteria. Finally, 22 studies were found that met our inclusion criteria and were consistent with our study objectives (references available). Figure 1 shows the flow chart of the studies included in this review.

Of the 22 studies included in this review, 17 assessed the starting treatment dose in children with CH. The characteristics of these 17 articles including study design, year of the study, participants, initial levothyroxine doses, follow up

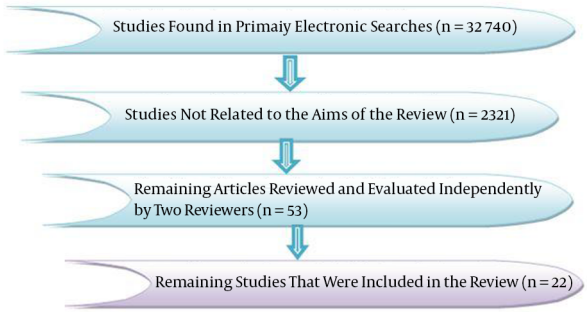

Figure 1. Flow Chart of Studies Assessed and Selected to be Included in the Review

duration, main outcomes and results are illustrated in Table 1.

As seen in Table 1, initial levothyroxine doses, for treatment of CH, evaluated in different studies varied between 3.21 and 23.6 μg/kg/d. The only clinical trial ever conducted in this area (17), demonstrated that by using a high dose at beginning of treatment (12 - 17 μg/kg/d), T4 and free T4 concentrations increased in the target range, three days after the treatment commenced; for normalization of TSH, the time required is a week. In other studies, several important outcomes such as mental developmental, psychomotor development etc. were assessed in order to evaluate the success of treatment related to various dosages of levothyroxine. Results of most studies favor using high doses at initiation of treatment. The study of Boileau et al. showed that infants treated with a dose of LT4 $\geq$ 6 μg/kg/d had a higher IQ performance (117.3 +/-1.8 vs. 112.8 +/- 1.2), in comparison with the results at doses < 6 μg/kg/d (18). In another study conducted by Dimitropoulos A, authors concluded that using 14.7 μg/kg/d at initiation of treatment led to significant higher IQ compared to the control group (111.4 versus 101.7; P < 0.0001) (19). Despite much data available in favor of using high doses, in one study it was mentioned that a dose of 3.21-5.81 μg/kg/d was adequate for the treatment of transient CH (20) and in another study elevated levels of FT4 were observed in many patients, showing that a systematic higher initial dosage could expose many children to the complications of hyperthyroidism (21).

Of the 22 studies included in this review, 13 studies assessed the time of initiation of treatment in hypothyroid infants. The characteristics of these 13 articles including study design, year of the study, participants, levothyroxine doses, follow up duration, main outcomes and results are summarized in Table 2.

Results summarized in Table 2 indicate that early detection and prompt treatment in the shortest possible time is very critically important part of CH treatment. Almost all the studies in Table 2 have consensus on early treatment, specifically in the first month of infants' lives. In this review however we found only one study reporting no correlations between initiation time of treatment and IQ or motor outcomes (22).

As mentioned in the evidence acquisition section, in this study we also evaluated risk of bias in articles that were entered in the review. For this, we used the STROBE check list, and for each study the probability of exist potentially confounders, selection bias and loss to follow up were examined. The results of critical appraisal for assessing risk of bias of studies are shown in Table 3.

4. Conclusions

In this study, we reviewed studies assessing the effects of initial dosage of levothyroxine and the timely initiation of treatment in children with congenital hypothyroidism. In general, 22 studies met our aims, of which in, 17 and 13 studies initial dosage and initiation time of treatment was discussed, respectively. It should be noted that 22 studies were included in the review whereas in some studies, both the subjects' starting dose and onset initiation time of treatment, were assessed simultaneously.

Regarding the use of a high dose at onset of treatment, although there is much evidence supporting treatment with a high dose (14), some studies not only showed that there are no adverse effects in using high dose thyroxine therapy bet also suggested better outcomes using higher childhood treatment doses (23). However, we found several studies that contradict these results, e.g. in a study conducted by Rovet in 1995, the authors showed that although the infants that received a higher dose of L-thyroxine at initiation of treatment, had better performances and indexes of intelligence, verbal ability, and memory, they also had more behavioural problems, including increased anxiety, poorer concentration and social withdrawal (24).

Although, neonatal screening for detection of congenital hypothyroidism has a history of over 35 years and today this program has been integrated in the public healthcare systems of most countries worldwide, in this systematic review we found no randomised clinical trial (RCT), except for one study (17), assessing and evaluating effects of different initial treatment dose on clinical outcomes, and most studies were cohort.

On the issue of time of initiation of treatment or, in other words, earlier onset of treatment, numerous studies have demonstrated the importance of early treatment of congenital hypothyroidism to prevent developmental defects. A few studies, however, have documented controversial results in this context, e.g. Kempers et al., who exam-

ined cognitive and motor functioning in 70 young adults with CH and median age at initial treatment of 28 days (range, 4 - 293 days), published in the journal of clinical endocrinology and metabolism, 2006, concluded that the severity of CH, and not the timing of treatment initiation, is the main factor determining long-term cognitive and motor outcomes (25).

In studies included in this systematic review, different outcomes were assessed, e.g. serum T4 and free T4, psychological development, hearing-speech performance scales, practical reasoning, pre-pubertal and pubertal growth, including anthropometric measurements, viz. height and intelligence quotient (IQ). Because of the large amount of outcomes examined and also due to the lack of homogeneity in the studies, running of any meta-analysis was not possible.

Overall, based on the results of our systematic review, we conclude that early detection is a fundamental key in dealing with congenital hypothyroidism; hence, there is no controversy or dispute regarding the issue of timing and initiation of treatment. Initiating treatment immediately after diagnosis and during the first days of life is absolutely imperative. However, in contrast with timing, we could not find strong evidence determining the precise optimal dosage of L-thyroxine to initiate treatment in children diagnosed with CH. Regarding the initial L-thyroxin (L-T4) dose, although both the American academy of pediatrics and the European Society for pediatric endocrinology recommend 10 - 15 μg/kg/day as the initial dose (26, 27), we still could not reach a definitive conclusion. Although, most studies included in our review favor using a high initial treatment dose (17, 28-33), some studies disagree. For instance, the study of Touati et al. found that a systematic higher initial dosage could expose many infants to complications of hyperthyroidism, whereas an initial dosage of 7.5 - 8.0 μg/kg per day, with early assessment of FT4, FT3, and TSH levels, is adequate for treatment of the majority of infants with CH (21). Hence, considering the results of previous studies, despite much evidence supporting the use of a high dose of levothyroxine at the start of treatment, we still could not conclude that treatment with high doses can be very helpful, but it can be said that treatment with very low doses could delay the normalization of thyroid hormones and occurrence of related complications. Hence further studies providing stronger evidence regarding this issue are required to reach a definitive decision.

Although the extensive search of databases worldwide and close examination of the available evidence are considered the strong point for this study, there were some potential limitations in this review. One limitation of this study was the lack of studies, especially studies with high level of evidence such as systematic reviews and meta-analyses, in this field. Also, because the studies investigating the optimal initiation levothyroxine dose and its initiation time of treatment in children with congenital hypothyroidism did not have identical methodologies, we were unable to conduct a statistical meta-analysis on these issues.

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Footnotes

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Table 1. Main Characteristics of the Studies That Assessed the Starting Dose in Congenital Hypothyroidism

First Author	Type and Year of the Study	No. of Participants	Initial Dose of Treatment	Follow Up Duration	Outcomes	Main Results and Conclusions of the Study
Selva et al. (17)	RCT (2002)	N = 47, (group 1= 15, group 2= 15 , and group 3= 17)	Group1:37.5μg/d, Group 2: 62.5 μg /d for 3 days then 37.5, Group 3: 50 μg/d	12 weeks	Time to normalization of TSH	T4 and free T4 concentrations increased to the target range (10 to 16 μg/dL) by the 3rd day of therapy in infants in groups 2 and 3 and by 1 week in group 1; 50 μg/day (average 14.5 μg/kg/day) provided the most rapid normalization of TSH by 2 weeks. Initial dosing of 50 μg/d (12 - 17 μg/kg/d) raised serum T4 and free T4 concentrations to within target range by 3 days and normalized TSH level by 2 weeks.
Selva et al. (34)	RCT (2005)	N = 47, No. of examined children = 31 (16 children lost)	Group1:37.5 μg /d, Group2: 62.5 μg /d for 3 days then 37.5, Group 3: 50μg/d	5 - 6 years	Neurodevelopme assessment (IQ)	However, verbal IQ, performance IQ, and achievement scores did not differ among the 3 treatment cohorts, subjects started on higher initial L-thyroxin doses (50 μg) had full-scale IQ scores; 11 points higher than those started on lower (37.5 μg) initial doses. On the other hand, children who were on higher initial dose of 50mcg/day L-thyroxin had higher full scale IQ scores compared to participants on lower initial dose of 37.5mcg/day.
Campos et al. (35)	Cohort (1995)	23	5.3 - 9.2 μg/kg/d (25 μg/ d)	59 months	Time to normalization of TSH, Neurodevelop-mental growth (IQ)	Serum T4 values increased (X = 11.4 +/- 2.7 μg/dL) within 4 weeks; TSH values remained elevated in 18 of 21 patients for 2-21 months, despite a high-normal T4. Mean Full Scale IQ for the CH group (n = 16) was 101.4 +/- 13.2 with comparable verbal and performance IQ scores. Patients with a bone age (BA) of $\leq$ 32 weeks or T4 < 2 μg/dL at initial evaluation had significantly lower verbal IQ scores. They concluded that (1) average range IQ scores and positive behavioral adaptation are observed in CH children treated with L-thyroxine doses below the currently recommended dose; (2) the L-thyroxin dose should be individualized to prevent iatrogenic hyperthyroidism; (3) TSH normalization should not be a primary objective of treatment.
Jones et al. (28)	Cohort (2008)	N = 314 , Group 1: n = 152; Group 2: n = 63; Group 3: n = 99	Group1: 25 mug, Group 2:30 - 40 mug, Group3: 50 mug	36 months	Normalization of thyroid function	An initial T4 dose of 50 ug daily, normalizes thyroid function several months earlier than lower dose regimes, with no evidence of sustained somatic overgrowth between 3 months and 3 years.
Yang et al. (20)	Cohort (2005)	N = 86, CH group: n = 57, Controls: n = 29	Treatment group: 3.21 - 5.81 μg/kg/d or 16.25 μg/d	24 to 36 months	Mental and physical development	A L-T4 dosage of 3.21 - 5.81 μg/kg/d was found to be sufficient for treatment of transient CH. Treated children showed overall satisfactory mental and physical development at age 2.
Touati et al. (21)	Cohort (1997)	N = 51 patients with CH	7.9 μg/kg per d	2 months	TSH measurements at 15 and 30 days of treatment	A mean dosage of 7.9 μg/kg per day at the onset of treatment and 6.6 μg/kg/d at 2 months, normalized FT4 and FT3 levels by day 15 day in 100% and TSH levels at 2 months in 90% of cases. Many patients showed elevated levels of FT4 and a systematic higher initial dosage could expose many infants to dangerous complications of hyperthyroidism. Even though a subgroup of patients, with abnormal TSH levels at 2 months, already had higher TSH levels in the first 8 weeks of life and, despite higher l-thyroxine dosage, also exhibited lower FT4 and FT3 levels, may require a higher dosage of l-thyroxine, an initial dosage of 7.5 - 8.0 μg/kg per day, with an early assessment of FT4, FT3, and TSH levels, is adequate for treatment of the majority of infants with CH.
Dickerman et al. (29)	Cohort (1997)	N = 30	8.5 μg /kg/d	11.4 years (at intervals of 1 - 6 months)	Pubertal growth (height)	Early detection and treatment of CH facilitates normal pre-pubertal and pubertal growth and achievement of normal adult height, following normal puberty. Adult height in CH is significantly correlated with parental height and the mean L-T4 daily dose administered over the first six months of treatment. A dose of at least 8.5 micrograms/kg/day is recommended during this period.

Bongers-Schokking et al. (30)	Cohort (2000)	61 (27 with severe CH and 34 with mild CH)	Patients treated with either a high initial dose of levothyroxine ($\geq$ 9.5 μg/kg/d) or a low initial dose (< 9.5 μg/kg/d)	10 to 30 months	Mental developmental index (MDI), and mean Psychomotor Developmental Index (PDI)	Mean $\pm$ SD MDI was 113 $\pm$ 14, and mean PDI was 114 $\pm$ 12. In the severe CH group, only patients treated early with a high initial dose had normal MDI scores (124 $\pm$ 16), whereas the scores of the other groups ranged from 97 to 103. In contrast, all patients in the mild CH group had normal scores (range, 122 - 125), except those in the group treated late with a low initial dose, with a score of 110 $\pm$ 10. Forty-three percent of the variance in MDI and PDI scores was explained by treatment factors, such as the treatment group, initial FT4 concentration, FT4-A, and FT4-B. The data suggest that optimal treatment includes achievement of euthyroidism before the third week of life by initiation of therapy with a levothyroxine dose 9.5 μg/kg/d.
Hrytsiuk et al. (36)	Systematic review (2002)	Between-study comparison = 14 cohort studies including 1321 patients. Within-study comparison = 4 cohort studies, including 558 patients.	-	-	-	Evidence on the effect of starting dose of levothyroxine on cognitive development is too weak to justify recommendations in favor of high or standard dose. They found no evidence for an effect of mean starting dose on mean IQ score.
Dubuis et al. (31)	Cohort (1996)	45 CH infants into 2 subgroups: 1, severe: n = 10; 2, moderate: n = 35	11.6 μg/kg/d	18 months	Neurodevelopme assessment (IQ)	With earlier treatment and a higher initial dose of levothyroxine, the early developmental outcome of infants with severe CH was the same as controls
Salerno et al. (32)	Cohort (2002)	83 CH patients: group 1 (n =42) group 2 (n = 21) Group 3 (n = 20)	Group 1: 6.0 - 8.0 μg/kg/d; Group 2: 8.1 - 10.μg/kg/d; Group 3:10.1 - 15 μg/kg /d	4 years	Neurodevelopment assessment (IQ)	IQ was significantly higher in group 3 (98 $\pm$ 9) compared to group 1 (88 $\pm$ 13; P < 0.05) but not compared to group 2 (94 $\pm$ 13); the results indicated that high LT4 starting doses rapidly normalize serum TSH concentrations resulting in an improvement of the IQ at 4 years of age, even in patients with severe CH. Growth and bone age maturation are not affected by such a high dose.
Simonau-Roy, et al. (37)	Cohort (2004)	Children with CH: 18 (9 severe and 9 moderate) Controls: 40	12 μg/kg/d	5 years	Neurodevelopme assessment (IQ)	The global IQs at 5 years and 9 months, were similar: medians (range) were 102 (87 to 133), 102 (84 to 135), and 115 (88 to 136) (not significant) for severe CH, moderate CH, and control children, respectively. Children with severe CH treated early with a high dose of levothyroxine had normal global development and behavior at school entry.
Dimitropoulos et al. (19)	Cohort (2009)	N = 238, CH groups: 63,controls: 175	14.7 μg/kg/ d (range 9.9 - 23.6 μg/kg/ d)	14 years	Neurodevelopment assessment (IQ)	IQ was significantly lower than controls after adjustment for socioeconomic status and gender (101.7 versus 111.4; P < 0.0001). Children with athyreosis had a lower IQ performance than those with dysgenesis (adjusted difference 7.6 IQ scores, P < 0.05). Lower initial T4 levels correlated with poorer IQ (r = 0.27, P = 0.04). Treatment during childhood was not related to IQ at age of 14 years. Adolescents with CH manifested IQ deficits when compared with their peers, despite early high-dose treatment and optimal substitution therapy throughout childhood. Adolescents with athyreosis and lower SES are at particular risk for adverse outcomes. Therefore, early detection of intellectual deficits is mandatory in children with CH.
Boileau et al. (18)	Retrospective study (2004)	N = 161, CH groups: 131, controls: 30	Mean initial dose of LT4:5.6+/-0.1 μg/kg/d	7 years	Neurodevelopme assessment (IQ)	No significant differences for IQ were observed with various initial LT4. Infants treated with a dose of LT4 $\geq$ 6 μg/kg/d had a higher performance IQ (117.3 +/-1.8 vs. 112.8+/- 1.2) compared with those treated with a dose of < 6 μg/kg/d. The severity of CH and socio-economic levels were similar in all groups. Timing appears to be a more important factor for the intellectual outcome.
Salerno et al. (38)	Cohort (2001)	55 (41 females and 14 males)	Greater than 8 μg/kg/d or lower than 8 μg/kg/d	17 years	Puberty	Girls treated with an initial dose of > 8μg/kg/day showed an earlier onset of puberty.

Germk et al. (39)	Cohort (1990)	43 patients with CH	10 to 14 μg/kg/d	1 year	Normalization of thyroid function.	They concluded that doses between 10 and 14 μg/kg/d are safe and effective for treatment of children with CH
Ilicki et al. (40)	Cohort (1991)	60 patients with CH	8.7 $\pm$ 2.8 μg/kg/d 15.0 $\pm$ 7.1 days	6.5 - 7.5 years	Normalization of biochemical indices	The findings indicate that a dose of 6 - 11 μg/kg/d is adequate and allows normal psychological development if treatment is started early. Compared with standard dosage regimens, a higher starting dose results in more rapid normalization of biochemical indices but the effect on development or growth is uncertain. They found no clear evidence that high-dose regimens improve development or growth.

Table 2. Main Characteristics of Studies Assessing Timing of Initiation of Treatment in Congenital Hypothyroidism

First Author	Type and Year of Study	No. of Participants	Start Time of Treatment	Follow Up Duration	Outcomes	Main Results and Conclusions of the Study
Kundu, et al. (41)	Comparative study (1996)	48	Group 1 included 18 children: thyroxine was started before and at 6 months of age. Group 2 included 30 children: thyroxine was started after 6 months of age	Unclear	Anthropometric measurements and IQ	In group 1, anthropometric measurements in the majority were in the 50th percentile or above. Their mental age was, on average, deficient by 5 months as compared to their chronological age and their IQ was > 85. In group 2, anthropometric measurements in the majority were below the 50th percentile. Their mental age was deficient on average by 14 months with IQ ranging between 50 and 70. Thyroxine therapy before 6 months of age considerably improved mental functioning to a level where they could be educated.
Chiesa et al. (42)	Comparative study (1994)	100	Group 1: < 2 months (n = 26); Group 2: 2-3 months (n = 13); Group 3: 3-6 months (n=21); Group 4: 6-12 months (n = 20); Group 5: 12-24 months (n = 20)	5 year	Anthropometric indices and bone age	Before treatment, groups 1 and 2 differed significantly from other groups in height ($P < 0.001$). With hormone therapy, catch-up growth was observed in groups 3 to 5; at age 5 no differences were found between groups. In all groups, height at 5 years of age correlated significantly with children's mid parental height ($P < 0.002$). Bone age was initially retarded in groups 3 to 5, but approximated the chronological age by age 5 years. Initially, HC was less affected than height and remained relatively larger, up to age 5 in all groups. These findings show that thyroid hormone replacement in CH even as late as 24 months corrects short stature and delayed bone age by the age of 5 years.
Bongers-Schokking et al. (30)	Cohort (2000)	61 (27 with severe CH and 34 with mild CH)	Patients treated either early (< 13 days) or late (≥ 13 days)	10 to 30 months	Mental developmental index (MDI), and mean psychomotor developmental Index (PDI)	Mean (± SD) MDI was 113 ± 14, and mean PDI was 114 ± 12. In the severe CH group, only patients treated early with a high initial dose had normal MDI scores (124 ± 16), whereas the scores of other groups ranged from 97 to 103. In contrast, all patients in the mild CH group had normal scores (range, 122 - 125), except those in the group treated late with a low initial dose, whose score was 110 ± 10; 43% of the variance in MDI and PDI scores was explained by treatment factors, such as the treatment group, initial FT4 concentration, FT4-A and FT4-B. The data suggest that optimal treatment includes achievement of euthyroidism before the third week of life by initiation of therapy before 13 days.
Dubuis et al. (31)	Cohort (1996)	45 CH infants into 2 subgroups: 1, severe: n = 10; 2, moderate: n = 35	Infants with median age of 14 days	18 months	Developmental outcome	With earlier treatment, the early developmental outcome of infants with severe CH was the same as controls.
Simoneau-Roy et al. (37)	Cohort (2004)	Children with CH: 18 (9 severe and 9 moderate) Controls: 40	Infants with median age of 14 days	5 years	Neurodevelopment assessment (IQ)	Global IQs at 5 years, 9 months, were similar: medians (range) were 102 (87 to 133), 102 (84 to 135), and 115 (88 to 136) (not significant) for severe CH, moderate CH, and control children, respectively. Children with severe CH treated early with a high dose of levothyroxine had normal global development and behavior at school entry.
Dimitropoulos, et al. (19)	Cohort (2009)	N = 238; CH groups: 63; controls: 175	Median age at onset of treatment was 9 d (range 5 - 18 d)	14 years	Neurodevelopme assessment (IQ)	IQ was significantly lower than in controls after adjustment for socioeconomic status and gender (101.7 versus 111.4; $P < 0.0001$). Children with athyreosis had a lower IQ performance than those with dysgenesis (adjusted difference 7.6 IQ scores, $P < 0.05$). Adolescents with athyreosis and lower SES were at particular risk for adverse outcomes. Therefore, early detection of intellectual deficits is mandatory in children with CH.

Lu et al. (43)	Cohort (2012)	N = 49	Patients were classified into two groups: < 1 month and 1 to 3 months of life	6 - 24 months	Physical and intelligence development	Treatment initiated below the age of 1 month of life contributes to improved physical and intellectual development, compared to treatment started between 1 and 3 months of life.
Boileau et al. (18)	Cohort (2004)	N = 161; CH groups: 131; controls: 30	Mean age at recall: 22.8+/-1.1 days.	7 years	Neurodevelopme assessment (IQ)	Optimal global IQ (GIQ; 119+/-1.8) was obtained for a recall of $\leq$ 15 days. Results for a recall after 3 weeks were lower (107.7 +/- 2.4). The IQ of infants treated before 21 days (117.1 +/-1.2) was identical to the IQ of those treated after this threshold (108.6 +/- 1.7). Timing appears to be a more important factor for the intellectual outcome.
Salerno et al. (38)	Cohort (2001)	55 (41 females and 14 males)	25+/-5 days	17 years	Puberty	Their results showed that conventional management of children with CH leads to normal sexual development and normal adult height.
Kempers et al. (22)	Cohort, (2007)	N = 82	Median age of 20 d	10.5 year	Cognitive and motor outcome (IQ and etc.)	No correlations were found between initiation time of treatment and IQ or motor outcomes. Advancing initiation of T4 supplementation from 28 to 20 d after birth did not result in improved cognitive or motor outcomes in CH-T patients.
Glorieux et al. (44)	Cohort (1983)	CH groups:45, controls: 37 assessed at age 12 months; CH groups:77; controls: 41 assessed at age 18months; CH groups: 59; controls: 40 assessed at age 12 months	Mean age of 27 d	36 months	Rate of development (with Griffiths Mental Development Scales)	At the age of 12 months, no statistically significant differences in the various test scores between the two groups were reported, but at age 18 and 36 months, the hypothyroid infants had lower scores in hearing-speech performance scales and practical reasoning (36 months), which also decreased their global quotient.
Germak et al. (39)	Cohort (1990)	43 patients with CH	Between 40 and 80 days	1 year	Normalization of thyroid function	They concluded that the prompt restoration of clinical and biochemical euthyroidism during early infancy is a safe and effective method for treatment of children with CH.
Ilicki et al. (40)	Cohort (1991)	60 patients with CH	15.0 $\pm$ 7.1 days	6.5 - 7.5 years	Normalization of biochemical indices	The findings indicate that if treatment is started early, a replacement dose of 6 - 11 μg /kg/d is adequate and allows normal psychological development.

Table 3. Risk of Bias in Studies Evaluating Initial Dose of T4 and Initiation Time of Treatment of Children With Congenital Hypothyroidism (Author's Judgment)[a]

Row	First Author	Year of the Study	Selection Bias	Confounder Bias	Loss to Follow Up Bias
1	Selva et al.	(2002)	+	?	+
2	Selva et al.	(2005)	+	?	-
3	Campos et al.	(1995)	-	-	+
4	Jones et al.	(2008)	+	+	+
5	Yang et al.	(2005)	-	?	+
6	Touati et al.	(1997)	+	?	?
7	Dickerman et al.	(1997)	-	+	+
8	Bongers-Schokking et al.	(2000)	-	+	?
9	Hrytsiuk et al.	(2002)	+	+	+
10	Dubuis et al.	(2002)	-	?	+
11	Salerno et al.	(1996)	+	?	+
12	Simoneau-Roy et al.	(2004)	-	?	+
13	Dimitropoulos et al.	(2009)	+	+	+
14	Boileau et al.	(2004)	-	+	+
15	Salerno et al.	(2001)	-	?	+
16	Germk	(1990)	-	?	+
17	Ilicki et al.	(1991)	-	?	+
18	Kundu et al.	(1996)	-	+	+
19	Chiesa et al.	(1994)	+	?	+
20	Lu et al.	(2012)	-	?	+
21	Kempers et al.	(2007)	-	?	+
22	Glorieux et al.	(1991)	+	?	+

[a] +, Low probability of bias; -, high probability of bias; ?, unclear.