Starting dose of levothyroxine for the treatment of congenital hypothyroidism: a systematic review
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Authors' objectives
To determine the effect of levothyroxine sodium starting dose on cognitive development, growth or behaviour in children with congenital hypothyroidism, as identified by neonatal screening.

Searching
The Cochrane Controlled Trials Register, MEDLINE and EMBASE (to June 1999) were searched using the terms 'congenital', 'hypothyroid', 'myxedem*', 'cretin*', 'levothyrox*', 'l-thyrox*', 'drug', 'therap*', 'treatm*' and 'manag*'. There were no language restrictions. In addition, reference lists in review articles, relevant textbooks and expert committee reports were handsearched. Forward citation searches were conducted up to March 2000 for all studies that met the inclusion criteria.

Study selection
Study designs of evaluations included in the review
Cohort studies. The between-study comparison required studies of children with congenital hypothyroidism, as identified by neonatal screening, whose global or cognitive development had been assessed using a population-standardised measure. The within-study comparison required cohort studies of children with congenital hypothyroidism, as identified by neonatal screening, and had to include an analysis of either of the following: the relationship between starting dose and any measure of global or cognitive development or growth, adjusted for severity of hypothyroidism at diagnosis on the basis of serum T4 levels or bone age; the relationship between starting dose and any measure of behaviour.

Specific interventions included in the review
Studies investigating children with congenital hypothyroidism, as identified by neonatal screening, who were receiving a starting dose of levothyroxine.

Participants included in the review
Children with congenital hypothyroidism, as identified by neonatal screening, whose global or cognitive development had been assessed using a population-standardised measure. The children included in the review were aged between 1 and 14 years.

Outcomes assessed in the review
First, the authors compared standardised doses of levothyroxine treatment with the mean standardised development scores in cohorts with different starting doses of levothyroxine. Second, the authors sought studies that compared development growth or behaviour in children treated with different starting doses of levothyroxine within the cohort. The studies included in the within-study comparison had to address the potential confounding effects of severity of hypothyroidism at diagnosis.

How were decisions on the relevance of primary studies made?
Two independent reviewers determined whether the studies met the inclusion criteria.

Assessment of study quality
No formal assessment of validity was undertaken.

Data extraction
Two reviewers independently extracted the data. The data extracted included: the mean starting doses of levothyroxine; the number of patients identified with congenital hyperthyroidism; the number of patients excluded from developmental assessment and the reasons for exclusion; the number undergoing testing for IQ or developmental quotient (DQ); and the mean IQ or DQ score, at each age of assessment as per standardised scales.

Methods of synthesis
How were the studies combined?
In the between-study comparison, the mean IQ or DQ was plotted with the 95% confidence interval for each study, at each age, by order of starting. The studies were ranked according to the mean or median starting dose. The association between starting dose and mean IQ or DQ was investigated in a weighted linear regression analysis, after allowing for between-cohort variations, using a random-effects model. The studies were weighted by the inverse of the variance and the model included terms for the proportion of children followed up and the age at assessment.

In the within-study comparison, no quantitative analysis of the effect of the starting dose on development was undertaken.

How were differences between studies investigated?
Differences were discussed in the text of the review and in the text for each cohort. Each cohort was described specifically in graphs and tables. Within-study comparisons were discussed under development, growth and behaviour.

Results of the review
The between-study comparison used data from 14 cohort studies based on 1,321 patients. The within-study comparison was of 4 cohort studies based on 558 patients.

The between-study comparison found that the standardised mean IQ or DQ scores ranged from 990 to 115, but they were not associated with the mean starting dose of levothyroxine (P=0.48). The within-study comparison found that the effect of levothyroxine starting dose on cognitive development was inconsistent. There was weak evidence for an effect on growth (1 study) and on behaviour problems (1 study).

Authors' conclusions
The evidence of an effect of levothyroxine starting dose on cognitive development, growth or behaviour is too weak to justify recommendations in favour of high- or standard-dose regimens.

CRD commentary
The descriptions of the methods used to conduct the review were brief. The search appeared comprehensive. There was no formal assessment of the validity of the included studies. Limited study details were reported, although the authors discussed the results in an appropriate manner. The authors are correct in their call for further research using randomised controlled trials to help inform future practice.

Implications of the review for practice and research
Practice: Further research using a randomised controlled trial is required to inform treatment policies.

Research: Further research using a randomised controlled trial is required to inform treatment policies.

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