Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence

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CRD summary
This review evaluated the effectiveness of levothyroxine on pregnancy outcomes in women with normal thyroid function who tested positive for thyroid autoantibodies and concluded that treatment can attenuate the risks of miscarriage and pre-term birth. The authors’ conclusions reflect the evidence, but the evidence was very limited.

Authors' objectives
To evaluate the effectiveness of levothyroxine on pregnancy outcomes in women with normal thyroid function who test positive for thyroid autoantibodies.

This question was part of a wider review on the association between thyroid autoantibodies and miscarriage and pre-term birth (reported fully in the paper).

Searching
MEDLINE, EMBASE and SciSearch were searched without language restrictions to 2011 and The Cochrane Library (2011) was searched. Search terms were reported. Reference lists and review articles were examined for further studies.

Study selection
For the effectiveness part of the review, randomised controlled trials (RCTs) that assessed the effects on maternal and foetal outcomes of levothyroxine given to women with normal thyroid function who tested positive for thyroid autoantibodies were eligible for inclusion. Excluded were women with overt biochemical hypothyroidism or hyperthyroidism.

Some of the included women were scheduled to have in vitro fertilisation treatment. Doses of levothyroxine were 1μg/kg/day or a titrated dose with a mean levothyroxine dose of 49.7μg/day (standard deviation 14μg) in the treatment group.

Two independent reviewers carried out the study selection. Disagreements were resolved by consensus and by discussion with a third reviewer.

Assessment of study quality
Trial quality was assessed using the Jadad scale of randomisation, allocation concealment, blinding, intention-to-treat and follow-up (maximum score 5).

The authors did not state how many reviewers carried out the quality assessment.

Data extraction
The authors did not explicitly state how data were extracted from the RCTs. Data were presented as risk ratios (RR) and 95% confidence intervals (CI).

Three reviewers were involved in the data extraction.

Methods of synthesis
Risk ratios and 95% CIs were pooled in a fixed-effect meta-analysis. Statistical heterogeneity was assessed using $\chi^2$ and $I^2$.

Results of the review
Two RCTs (sample size reported as n=160 in the forest plot and n=187 in the text) were included in the meta-analysis. One trial was placebo-controlled. Follow-up was to the end of pregnancy. Jadad scores were 3 and 5.
Pooled results showed a statistically significant risk reduction for miscarriage (RR 0.48, 95% CI 0.25 to 0.92, $I^2 = 23\%$; two trials). Relative reductions in miscarriage rates were 36% and 75%. One trial (n=115) showed a statistically significant risk reduction for pre-term birth (RR 0.31, 95% CI 0.11 to 0.90).

No reported safety concerns arose from the treatment.

**Authors’ conclusions**

There was preliminary evidence that levothyroxine can attenuate the risk of miscarriage and pre-term birth in women with normal thyroid function who test positive for thyroid autoantibodies.

**CRD commentary**

The research question was clear in the context of a wider review. Inclusion criteria were presented clearly with potential for replication. The search strategy included relevant sources. Attempts were made to minimise language bias. Study selection and data extraction was conducted with some attempt to minimise error and bias; the review process was not clear for quality assessment. An appropriate validity assessment tool was used to rate the included studies and both were of acceptable quality. There was no justification for the pooling of only two RCTs.

The authors' conclusions reflected the evidence presented, but the evidence was very limited (acknowledged by the authors) in terms of small sample size, trials conducted in the same research centre and follow-up that would not have detected rare or long-term adverse events.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that a large placebo-controlled randomised trial was required to analyse live births as the primary outcome.

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