Antenatal thyrotropin-releasing hormone was associated with developmental delay in infants at 1 year


Objective
To determine the long-term effects of thyrotropin-releasing hormone (TRH) in infants whose mothers had been at high risk for preterm delivery and who had received TRH plus corticosteroids to prevent neonatal respiratory disease.

Design
1-year follow-up of a randomised, double-blind, placebo-controlled trial (Australian Collaborative Trial of Antenatal Thyrotropin-releasing Hormone [ACTOBAT]).

Setting
18 hospitals in Australia.

Patients
[Women with singleton or twin pregnancies were eligible if the duration of gestation was between 24 weeks and 31 weeks and 6 days and if they were judged to be at risk for preterm delivery and warranted corticosteroid treatment].

Main results
Multiple logistic regression analysis of the entire cohort (n = 1022) showed that treatment with TRH was associated with motor delay (odds ratio [OR] 1.51, 95% CI 1.11 to 2.05, P = 0.009); social delay (OR 1.40, CI 1.01 to 1.95, P = 0.04); and sensory impairment (OR 2.0, CI 1.06 to 3.74, P = 0.03). TRH was not associated with greater achievement in any of the milestones.

Conclusion
Thyrotropin-releasing hormone given to mothers at risk for preterm delivery was associated with developmental delay at 12 months.

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Commentary
Studies from the early 1970s showed that antenatal steroids could prime the fetal lung, reducing the respiratory problems associated with preterm birth. Further, animal studies suggested that thyroid hormones could enhance that effect and that it could probably apply to human pregnancy. 5 trials between 1989 and 1994 supported this finding but only examined babies delivered 2 to 10 days after treatment. However, when the ACTOBAT Trial Group examined the results for all the children in this trial, no evidence of benefit was found. A systematic review of all trial data showed that modest improvements in respiratory outcome for those babies delivered shortly after treatment were offset by unexpectedly worse outcomes among those delivered later (1). 2 other studies only as yet published in abstract form have strengthened these conclusions (2, 3).

The ACTOBAT Trial Group now presents evidence showing that developmental outcome may be worse after antenatal TRH. There will be criticism of the data on which this conclusion is based, but it should more justly be directed at the funding bodies who would have been easier if the test inventory were expanded. It should be of biologically plausible: Brief reactive fetal hypothyroidism could have a diffuse effect on early behaviour and later development. A plausible treatment strategy backed by sound experimental evidence has now been discredited. There is nothing to suggest that the low dose of TRH used in the ACTOBAT trial had anything to do with its failure to confirm the outcome of earlier studies. This important study reminds us that small trials that only examine early outcomes in a selected group of patients can be seriously misleading, especially if they fail to examine long-term outcomes.

Edmund Hey, DNM
Newcastle upon Tyne, England, UK

References