Effectiveness of prenatal treatment for congenital toxoplasmosis: a meta-analysis of individual patients' data
Thiebaut R, Leproust S, Chene G, Gilbert R

CRD summary
This review of individual patient data evaluated the effect of prenatal treatment for congenital toxoplasmosis on mother-to-child transmission and infants' clinical manifestations. Treatment was associated with a lower rate of mother-to-child transmission, but did not change the risk of clinical manifestations. The authors stated that randomised clinical trials are needed to confirm these findings. These conclusions are likely to be reliable.

Authors' objectives
To estimate the effects of prenatal treatment for congenital toxoplasmosis on the risk of mother-to-child transmission of infection and clinical manifestations during infancy, with an individual patient data (IPD) meta-analysis.

Searching
MEDLINE, EMBASE and Pascal were searched from 1980 to 2002. The search was updated through Current Contents in November 2005. The reference lists of identified papers were checked and experts in the field were contacted for additional studies. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
This review included IPD from observational cohorts.

Specific interventions included in the review
The inclusion criteria relating to the intervention were not explicitly stated, although it was clear that prenatal treatment for toxoplasmosis was the focus of the review. The prenatal treatment strategies considered in the review included no treatment, spiramycin, pyrimethamine-sulphonamides, and spiramycin followed by pyrimethamine-sulphonamides. The doses and regimens of prenatal treatments were not reported. In cases of missing information about type or timing of treatment, the authors assumed that treatment was provided as stated in the study protocol.

Participants included in the review
Studies of pregnant women screened positive for Toxoplasma gondii infection during pregnancy by universal screening were eligible for inclusion. Cohort studies with retrospective testing for maternal infection were excluded. The precise dates of testing and start of prenatal treatment were required for a study to be included. Studies of mothers enrolled before 1985 were excluded. For the analyses of clinical manifestations in children, only European cohorts of liveborn children with congenital toxoplasmosis were considered.

Outcomes assessed in the review
Studies assessing mother-to-child transmission and/or infants' clinical manifestations were eligible. Clinical manifestations were defined as ocular lesions, intracranial lesions, or both, and to be eligible, studies of clinical manifestations had to perform at least one ophthalmoscopy or intracranial imaging examination during the first year of life.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies. The authors did not state whether trial investigators were contacted to verify uncertain eligibility.

Assessment of study quality
The authors did not state how and whether any inconsistency or missing data were verified with the trial investigators. Four reviewers examined the IPD before deciding whether to include a trial.

**Data extraction**
The authors did not state whether trial investigators were contacted to verify the finalised data.

**Methods of synthesis**

**How were the studies combined?**
Pooled odds ratios (ORs) and their confidence intervals (CIs) were calculated using a fixed-effect logistic regression model and checked with a random-effects model. Only results obtained with the fixed-effect model were presented since the use of the random-effects model did not modify the findings. An integrated maximum likelihood method was used to account for gestational age at seroconversion and timing of treatment initiation.

**How were differences between studies investigated?**
The effect of gestational age at seroconversion, the latitude of the centre, and the period during which the study was conducted (before 1991, between 1991 and 1994, and after 1994) on the pooled estimates was considered in the analysis using the likelihood ratio test. The effect of timing and type of prenatal treatment was examined in subgroup analyses. Sensitivity analysis was performed to test the robustness of the results by the method used to estimate the gestational age at seroconversion.

**Results of the review**
The IPD from 14 studies (including IPD for 20 cohorts of 1,721 women and 26 cohorts of 550 infants) were included in the review. The authors stated that other eligible trials were identified, but one trialist refused to participate and the investigators of 4 studies did not respond.

**Mother-to-child transmission.**

The risk of mother-to-child transmission increased with gestational age at seroconversion (OR 1.15 per week, 95% CI: 1.12, 1.17). Prenatal treatment was associated with a lower risk of transmission (OR 0.94 per week, 95% CI: 0.90, 0.98), especially when treatment was started early after the mother's seroconversion. The odds of transmission also decreased significantly with higher (5 degrees) latitude (OR 0.71, 95% CI: 0.53, 0.96). Rates of mother-to-child transmission were not significantly different when patients were treated with spiramycin compared with pyrimethamine-sulphonamide (OR 0.79, 95% CI: 0.55, 1.13). Clinical manifestations.

Higher gestational age at seroconversion was associated with a lower risk of overall clinical manifestations (OR 0.96 per week, 95% CI: 0.93, 0.99, p=0.01), intracranial lesions (OR 0.91 per week, 95% CI: 0.87, 0.95) and ocular lesions (OR 0.97 per week, 95% CI: 0.93, 1.00, p=0.04) in infancy. The risk of any clinical manifestations was comparable between infants of treated and untreated mothers (OR 1.11, 95% CI: 0.61, 2.02). Correcting for the type of treatment, period of the study, or the latitude of the centre did not modify these findings. The combination of spiramycin and pyrimethamine-sulphonamide carried a higher risk of any clinical manifestations than pyrimethamine-sulphonamide alone (OR 1.29, 95% CI: 1.42, 9.34).

**Authors' conclusions**
Prenatal treatment appears to carry a lower risk of mother-to-child transmission, but does not seem to decrease the risk of clinical manifestations in infected liveborn infants. A large randomised controlled trial would be needed to confirm these findings.

**CRD commentary**
This meta-analysis of IPD addressed a well-defined question in terms of the participants, outcomes and study design, while it used a broad definition for the intervention. The authors searched several bibliographic databases without
language restrictions and made efforts to identify additional unpublished trials, although they did not assess publication bias. It is unclear whether trialists were contacted to check each trial’s eligibility and whether checking, validation and reanalysis of raw data from the included clinical trials were conducted. The number of excluded studies, as well as the number of participants in trials for which data could not be retrieved, were specified. At least two reviewers made decisions about inclusion and exclusion and the criteria used for study selection were reported. It is not clear whether statistical heterogeneity was assessed. The data appear to have been analysed using appropriate techniques for the meta-analysis of IPD. Although the reporting of the methods of this review is lacking in some areas, the authors’ conclusions appear appropriate and, based on the evidence presented, are likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that large randomised clinical trials are needed to clarify the real benefit of prenatal treatment, both within and outside Europe.

Funding
Part of the Eurotoxo project, which is funded by the European Commission, contract number QLG4-CT-2002-30262.

Bibliographic details

PubMedID
17223474

DOI
10.1016/S0140-6736(07)60072-5

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Coccidiostats /therapeutic use; Europe; Female; Gestational Age; Humans; Infant, Newborn; Infectious Disease Transmission, Vertical; Logistic Models; Pregnancy; Pregnancy Complications, Parasitic /diagnosis /drug therapy /physiopathology; Prenatal Diagnosis /economics /methods; Spiramycin /therapeutic use; Toxoplasmosis, Congenital /diagnosis /drug therapy /transmission; Treatment Outcome

AccessionNumber
12007000587

Date bibliographic record published
31/01/2008

Date abstract record published
31/01/2008
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.