Antepartum or postpartum isoniazid treatment of latent tuberculosis infection
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Three strategies for treating latent tuberculosis (TB) in pregnant women aged less than 35 years were examined. The treatment options were antepartum isoniazid (300 mg/day isoniazid with pyridoxine beginning at 20 weeks’ gestation for 6 months), postpartum isoniazid (300 mg/day isoniazid with pyridoxine for 6 months after delivery) and no treatment.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population consisted of women aged 20 years with a positive (greater than 10 mm) tuberculin skin reaction and a negative chest radiograph obtained at 20 weeks' gestation.

Setting
The setting was unclear, although it is likely to be representative of secondary care. The economic analysis was conducted in Durham (NC), USA.

Dates to which data relate
The effectiveness evidence and resource data were derived from studies published between 1978 and 2002. The prices used were for 1998.

Source of effectiveness data
The effectiveness evidence was derived from a non-systematic review of published studies, which was augmented by the authors' assumptions.

Modelling
A published Markov decision-analysis model was adapted in order to estimate the costs and outcomes of the three strategies. The authors validated the model by comparing the age-specific estimates of the outcomes to the original model. The hypothetical cohort of women was followed up until age 85 years. Further details of the model were reported elsewhere (see Other Publications of Related Interest).

Outcomes assessed in the review
The treatment effect outcomes assessed in the review and used as model inputs were the efficacy of isoniazid and the
relative risk (RR) of isoniazid-induced hepatitis during pregnancy. Other epidemiological variables obtained from the
review were reported in full in the paper. It appears that adverse effects have not been included in the model.

Study designs and other criteria for inclusion in the review
Not stated.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
Seventeen studies were included in the review.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not stated.

Results of the review
The main results of the review were as follows.

The efficacy of a complete course (6 months) of isoniazid was 67% (range: 50 - 98), and that of an incomplete course
(3 months) was 15% (range: 10 - 30).

The probability of completing a course of isoniazid was 20% (range: 10 - 50).

The RR of isoniazid-induced hepatitis during pregnancy was 2% (range: 1 - 5).

Other epidemiological variables and ranges were reported in full in the paper. The authors stated that estimates that
would bias the analysis against antepartum treatment were chosen.

Methods used to derive estimates of effectiveness
The authors extrapolated the RR of incomplete treatment and death in hepatitis survivors. They also made several
assumptions.

Estimates of effectiveness and key assumptions
The authors estimated the RR to be 1 (range: 1 - 3) for incomplete treatment and 1 (range: 1 - 2) for death in hepatitis
survivors. They assumed that all hepatitis survivors had the same degree of risk of TB as patients who received an
incomplete course of therapy. In addition, they assumed that would be no foetal death in women who develop hepatitis,
and that isoniazid-associated hepatitis would not result in excessive foetal mortality rates.

**Measure of benefits used in the economic analysis**
The benefit measure used in the economic analysis was the life-years saved. The benefits were discounted at a rate of 3%. Other intermediate model outcomes were predicted cases of TB within the cohort, cases of secondary to horizontal transmission, and cases of fatal and nonfatal hepatitis.

**Direct costs**
Only the direct medical costs were considered. These included the cost of treatment for latent TB infection, and the cost of diagnosis and treatment of active TB. Non-medical costs and costs associated with TB cases secondary to horizontal transmission were excluded. In addition, the authors chose not to include the costs associated with horizontal transmission, as there were no reliable estimates for them in the paediatric population and they would favour the antepartum treatment. The costs were estimated from published studies. All of the costs were converted using the medical care consumer price index. The prices for 1998 were used. The unit costs and the quantities were not reported separately. The costs were discounted at an annual rate of 3%.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
No indirect costs were reported.

**Currency**
US dollars ($).

**Sensitivity analysis**
One-way sensitivity analyses were conducted on all model inputs, including the costs and discount rates. The variables were varied over the ranges obtained from the literature review. In addition, a worst-case scenario analysis was performed using estimates at the extremes of the ranges.

**Estimated benefits used in the economic analysis**
The base-case scenario resulted in a discounted life expectancy of 26.7 years (undiscounted 57.1 years) for all three treatment options.

**Cost results**
The total cost associated with antepartum treatment was $22.4 million when discounted at a rate of 3%. The undiscounted total cost was $35.9 million.

The total cost associated with postpartum treatment was $34.4 million when discounted at a rate of 3%. The undiscounted total cost was $50.1 million.

The total cost associated with no treatment was $44.2 million when discounted at a rate of 3%. The undiscounted total cost was $75.1 million.

The incremental costs were not reported.
Synthesis of costs and benefits
For the base-case scenario, antepartum treatment was found to be the dominant treatment strategy.

In a sensitivity analysis with a case-fatality rate for TB of 0.1%, the authors reported an incremental cost-effectiveness ratio (ICER) of $479,198 per life-year saved (discounted) for postpartum treatment compared with antepartum treatment. The ICER was $1.324 million per life-year saved for no treatment compared with antepartum treatment.

The results showed that antepartum treatment would only become the least advantageous strategy if the case-fatality rate for TB were ten times lower than the base-case and the risk of fatal hepatitis ten times higher.

Authors' conclusions
From a public health perspective, antepartum treatment would result in fewer cases of TB and would be the most cost-effective treatment.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator (no treatment) was clear. You should decide if it represents a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The majority of estimates were obtained from a review of the literature. However, a systematic review was not undertaken and no search details were reported. In addition, the inclusion and exclusion criteria for the primary studies were not reported and it would appear that they had been used in an ad-hoc manner. There were no details on the methods used to combine the studies, whether a synthesis was conducted, or if the impact of differences between the studies was assessed. The authors made several assumptions and although these were tested in sensitivity analyses, it was unclear whether the ranges chosen were optimal. Adverse effects were not included. The authors stated that this was due to the lack of an identifiable syndrome or estimation of the potential congenital anomalies associated with isoniazid.

Validity of estimate of measure of benefit
The benefit measure was the life-years saved. A more appropriate measure of benefits, including an assessment of quality of life, would have been relevant for a broader comparison of the benefits of treatment alternatives for latent TB infection in pregnancy. However, the authors reported that no validated data were available on quality of life for TB and isoniazid-related hepatitis states. A major question emerges with the calculation of ICERs. Given the very small marginal gains and the very high marginal costs obtained when the alternatives were compared, the additional cost per additional year of life saved using the postpartum strategy in comparison with the antepartum strategy should be extremely high (several million of dollars). This was not reflected in the results. The authors also stated that, for the base-case, estimates that would bias the results against the antepartum treatment were chosen. The reason for this choice was not justified.

Validity of estimate of costs
The perspective adopted for the economic analysis was that of the health care system. It would appear that all the relevant costs have been included. The authors justified not adopting a broader societal perspective on the grounds of insufficient data on non-medical costs. The costs associated with horizontal transmission in the paediatric population were not included, due to a lack of reliable data. The authors acknowledged that this omission would have favoured the postpartum strategy. The costs and the quantities were not reported separately, which may limit the reproducibility of the study in other settings. Discounting was conducted and the rate investigated in a sensitivity analysis.

Other issues
The authors did not compare their findings with those from other studies. In addition, they failed to address the issue of
generalisability to other settings or countries. The authors reported no further limitations of their study. The results appear to have been reported selectively and not everything was reported clearly.

**Implications of the study**
Rather than delaying treatment until postpartum, the antepartum treatment of latent TB during pregnancy should be considered. If isoniazid is not administered antepartum, then efforts to improve postpartum compliance should be instituted since either antepartum or postpartum treatment is better than no treatment.

**Source of funding**
None stated.

**Bibliographic details**

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11042314

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
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