Acyclovir prophylaxis for pregnant women with a known history of herpes simplex virus: a cost-effectiveness analysis

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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
The study examined prophylactic antiviral (acyclovir) therapy for women with a history of herpes simplex virus (HSV) but without recurrence during pregnancy.

Type of intervention
Secondary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of pregnant women with a history of diagnosed HSV but without recurrence during pregnancy.

Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data came from studies published between 1983 and 2004. The price year was 2005.

Source of effectiveness data
The effectiveness data were derived from a review of published studies, augmented by some authors’ assumptions.

Modelling
A decision tree model was developed, using TreeAge Pro software, to estimate the clinical benefits and costs of acyclovir prophylaxis in the study population. The model considered the probability of experiencing side effects with acyclovir therapy. In case of HSV transmission, the health outcomes included were normal neonate, moderately impaired neonate, severely impaired neonate and neonatal death. A moderately impaired neonate was defined as a child who could perform the activities of daily living on his own, free from pain, and who performed schoolwork more slowly than his peers. A severely impaired neonate was defined as a child who needed assistance with eating, bathing or using the toilet, was very slow at schoolwork, was in moderate to no physical pain, and was blind, deaf or unable to talk. The time horizon of the model seems to have been the child’s lifetime, although it was not explicitly reported.

Outcomes assessed in the review
The effectiveness outcomes assessed for use in the model were:
the genital HSV infection because of HSV Type 1;
the probability of side effects because of acyclovir therapy;
the probability of a Caesarean delivery if no lesions were present;
the maternal mortality rate;
the probability of lesions at delivery;
the probability of shedding asymptotically at delivery;
the probability of neonatal transmission if shedding;
the outcomes of neonatal transmission (probabilities of moderate or severe neurologic disability and probability of neonatal death); and
the effectiveness of acyclovir.

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

Sources searched to identify primary studies
Not reported.

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

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

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

Methods of combining primary studies
The authors used composite odds ratios determined by meta-analysis to reduce the probabilities of either having lesions or asymptomatic shedding with acyclovir prophylaxis. No more information was given about the method of combining primary studies for the rest of the probabilities obtained in the review. However, combination was not necessary in most cases since each probability was derived from only one source.

Investigation of differences between primary studies
Not reported.

Results of the review
The probability of genital HSV infection because of HSV Type 1 was 0.150.

The probability of side effects because of acyclovir therapy was 0.020.
The probability of a Caesarean delivery if no lesions were present was 0.244.

The probability of maternal death was 0.000092 with vaginal delivery, 0.000350 with Caesarean delivery not for lesions, and 0.000239 with Caesarean delivery for lesions.

The probability of lesions at delivery was 0.0037 with HSV-1 and 0.0110 with HSV-2.

The probability of shedding asymptomatically at delivery was 0.0018 with HSV-1 and 0.0055 with HSV-2.

The probability of neonatal transmission if shedding was 0.00 with Caesarean delivery for lesion. For all other deliveries, the probability was 0.28 for neonatal HSV-1 if maternal HSV-1, 0.113 for neonatal HSV-2 if maternal HSV-1, 0.000 for neonatal HSV-1 if maternal HSV-2, and, 0.040 for neonatal HSV-2 if maternal HSV-2.

The probability of moderate neurologic disability was 0.01 for HSV-1 and 0.14 for HSV-2.

The probability of severe neurologic disability was 0.02 for HSV-1 and 0.17 for HSV-2.

The probability of neonatal death was 0.28 for HSV-1 and 0.20 for HSV-2.

The effectiveness of acyclovir in reducing lesions was 0.75.

The effectiveness of acyclovir in reducing asymptomatic shedding was 0.91.

The effectiveness of acyclovir in reducing transmission was 0.89.

Methods used to derive estimates of effectiveness
The authors made an assumption in order to complete all the probabilities of the model.

Estimates of effectiveness and key assumptions
It was assumed that if lesions were present at time of delivery, every child would be delivered by Caesarean.

Measure of benefits used in the economic analysis
The measure of benefit was the quality-adjusted life-years (QALYs). The QALYs were obtained from the literature. Only the mothers' and children's QALYs estimates were taken into consideration. In calculating the mothers' QALYs, the USA average maternal age and life expectancy were used. To calculate the maternal utility decrease when a child had either moderate or severe neurologic impairment, the authors used the estimated utility for having a child with Down syndrome. For a neonate with neurologic disability, the life expectancy of a child with either severe or moderate cerebral palsy was used. For the utility of being a child with either severe or moderate neurologic disability, the estimates from Saigal et al. (see 'Other Publications of Related Interest' below for bibliographic details.) were used. Discounting was applied at a rate of 3%. Moreover, the number-needed-to-treat was calculated for several outcomes (Caesarean deliveries, neonatal deaths and severely neurologically impaired children).

Direct costs
The direct costs included were for acyclovir prophylaxis, vaginal delivery, Caesarean delivery, Caesarean delivery for lesions, the initial hospital treatment for neonate with HSV, and the lifetime treatment of a child with moderate or severe neurologic disability. For the lifetime cost of having a child with severe neurologic disability, the cost of a child with cerebral palsy was used. The costs, which were obtained from the literature, reflected real costs rather than charges. The costs and the quantities were not reported separately. The price year was 2005. It was not reported whether discounting was applied.

Statistical analysis of costs
The costs were treated deterministically in the base-case.

**Indirect Costs**
The indirect costs were not considered.

**Currency**
US dollars ($).

**Sensitivity analysis**
The robustness of the model results were tested by varying every variable of the model (univariate sensitivity analysis). Moreover, threshold analyses were performed over particularly sensitivity inputs. Finally, a Monte Carlo simulation was used to test the robustness to simultaneous multivariable changes in a theoretic cohort of 160,000 women. Triangular distributions were used for the Monte Carlo simulations.

**Estimated benefits used in the economic analysis**
The average composite QALY for mother and child was 56.7117 with acyclovir versus 56.7074 with 'no acyclovir'. The total number of QALYs (in thousands) in the 160,000 women cohort was 9,074 with acyclovir versus 9,073 with 'no acyclovir'.

The clinical outcomes showed that 22,286 women needed to be treated to prevent 1 neonatal death, 8,985 women needed to be treated to prevent 1 affected child, and 177 women needed to be treated to prevent 1 Caesarean delivery.

**Cost results**
The average cost per woman was $6,102 with acyclovir and $6,122 with 'no acyclovir'.

The respective figures for the 160,000 women cohort were $976 million (with acyclovir) versus $979 million (without acyclovir).

**Synthesis of costs and benefits**
Acyclovir prophylaxis was a dominant strategy since it was both less expensive and more effective than the option of no prophylaxis. Therefore, cost-effectiveness ratios were not calculated. Acyclovir prophylaxis saved approximately $20 per person and increased the total QALYs by 0.01. By providing acyclovir prophylaxis to a hypothetical cohort of 160,000 women, approximately $3 million were saved and 1,000 QALYs were gained. Moreover, it prevented approximately 6 severely neurologically impaired children, 7 neonatal deaths and 1,000 Caesarean deliveries.

These results proved to be robust in the univariate sensitivity analyses. Threshold analyses showed that acyclovir was the dominant strategy up to a cost estimate of $67 (150% of baseline). The Monte Carlo simulation demonstrated acyclovir to be cost-effective (at a cost of <$20,000 per QALY) 100% of the time and cost-saving greater than 99% of the time.

**Authors' conclusions**
Acyclovir prophylaxis was not only cost-effective but also cost-saving for pregnant women with a diagnosed history of genital herpes who do not experience recurrence during pregnancy.

**CRD COMMENTARY - Selection of comparators**
The comparator was standard care which did not include drug therapy. However, it would have been interesting to have compared acyclovir with other antiviral therapies available on the market. You should decide if the options evaluated (acyclovir prophylaxis versus no prophylaxis) are relevant in your own setting.
Validity of estimate of measure of effectiveness
The effectiveness evidence was derived from the literature. As a systematic review of the literature was not reported, it was not clear whether all of the relevant studies were included. However, every effectiveness input used in the model was tested in the sensitivity analyses, which to some extent enhance the validity of the results obtained. Despite this, given the lack of detail on the methods used to identify and select the studies from which the model inputs were derived, it was difficult to ascertain if the best available evidence had been used in the analysis.

Validity of estimate of measure of benefit
The use of QALYs as a measure of benefit enables the results to be compared with those of other studies. The utilities rates were obtained from the literature and most of them were not specific for the health states analysed in the model (i.e. the utilities for having a child with Down syndrome or the life expectancy of a child with cerebral palsy were used). The QALYs were discounted appropriately. As the authors stated, it is most likely that the QALYs estimates were underestimated because they only included the mother and the child and ignored the impact of other members of the family.

Validity of estimate of costs
It seems that all the categories of costs relevant to the perspective adopted have been considered in the study. The quantities and the costs were not reported separately. However, the price year was stated and comprehensive sensitivity analyses were performed. These, in some degree, enhance the possibility of replicating the study in other settings. It was unclear whether the costs were discounted, although it would have been appropriate since lifetime costs were considered in the model. Real costs rather than charges were used.

Other issues
The issue of generalisability was not explicitly addressed, although the results obtained seem to have been quite specific to the setting where the study was carried out. Further details on resource use and the costing methodology would have been helpful (it would have been particularly useful to have had evidence that the costs were discounted). The authors made some comparisons of their findings with those of other studies and it seems that similar conclusions were found.

Implications of the study
The study findings suggested that, compared with no treatment, the use of acyclovir prophylaxis for pregnant women with a diagnosed history of genital herpes who do not experience recurrence during pregnancy is cost-effective over a wide range of assumptions. The authors recommended that further studies should be done on other populations, since most neonatal infections were not addressed in this study. Most of the neonates who are born with HSV are delivered by women without a known history of genital HSV.

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Other publications of related interest

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