Cost-effectiveness of herpes simplex virus type 2 serologic testing and antiviral therapy in pregnancy

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 the screening and further treatment of herpes simplex virus Type 2 (HSV-2) in pregnant women were examined.

Strategy 1 was no test.

Strategy 2 was to test pregnant women only.

Strategy 3 was to test pregnant women and partners of those women who test HSV-2 seronegative.

The strategies were described in detail.

Type of intervention
Screening.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of pregnant women.

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

Dates to which data relate
The effectiveness data were estimated from studies published between 1983 and 2004. Some cost and resource use data were estimated from sources published between 1983 and 2004. The price year was 2003.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and authors' opinions.

Modelling
A decision tree model was constructed to compare the outcomes in a population of 100,000 pregnant women with and without different testing scenarios for HSV-2 infection. The time horizon of the model was neonatal lifetime. The structure of the decision tree for the no test strategy was depicted graphically.
Outcomes assessed in the review
The outcomes estimated from the literature were:

- the probability values associated with pregnancy and delivery procedures,
- the prevalence of HSV-2,
- the sensitivity and specificity of HSV-2-specific tests,
- the infection rates,
- the uptake of antiviral suppressive therapy (AST) and compliance rates,
- life expectancy, and
- utility weights.

Study designs and other criteria for inclusion in the review
It appears that a non-systematic review of the literature was undertaken to identify the primary studies. Limited information on the design of the studies was provided. Expected survival came from US life tables. The utility values were estimated from a study that used the EuroQol.

Sources searched to identify primary studies
MEDLINE was searched for primary studies.

Criteria used to ensure the validity of primary studies
In general, the authors chose the most recent data available.

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

Number of primary studies included
Twenty-nine primary studies provided evidence.

Methods of combining primary studies
A narrative approach appears to have been used to combine most of the primary estimates.

Investigation of differences between primary studies
Not stated.

Results of the review
The probability that a pregnant woman was HSV-2 positive was 26%.

The probability that a pregnant HSV-2 positive woman had had a diagnosis of genital herpes was 9.2%.

The probability that the partner of a pregnant HSV-2 negative woman was HSV-2 positive was 14% (alternative value 17.8%).
The sensitivity of the HSV-2-specific test was 98% (alternative values 97% and 100%) and the specificity was 97% (alternative values 94% and 98%).

The probability that the partner of a pregnant woman was willing to be tested was 75% (alternative value 25%).

The probability that a pregnant woman accepting AST from week 36 was compliant was 82% (alternative values 75% and 90%).

The probability that a HSV-2 negative pregnant woman acquires a new HSV-2 infection between 15 and 40 weeks of pregnancy was 4.13% (alternative values 2.00% and 6.7%).

The rate of reduction in transmission of HSV-2 infection from an HSV-2 positive partner to an HSV-2 negative woman caused by AST was 48%.

The rate of lesions at delivery for HSV-2 positive pregnant woman with a diagnosis of genital herpes and no suppression was 14.5% (alternative value 20%).

The rate of lesions at delivery for an HSV-2 positive pregnant woman without a diagnosis of genital herpes and no suppression was 6% (alternative value 3.14%).

The rate of lesions at delivery for a pregnant woman with HSV-2 infection newly diagnosed after week 32 was 34%.

The rate of asymptomatic shedding at delivery for an HSV-2 positive or HSV-2 infected but negative pregnant woman with no suppression was 1.60% (alternative values 0.5% and 3.3%).

The rate of reduced risk of lesions or asymptomatic shedding for HSV-2 positive pregnant women with AST was 80% (alternative values 50% and 90%).

The rate of lesions detected at delivery by a screening programme was 90% (alternative values 80% and 99%).

The rate of Caesarean delivery in the general population was 22%.

The rate of Caesarean delivery if lesions were present at delivery was 85% (alternative values 78.6% and 100%).

The rate of no NH in the case of Caesarean delivery in HSV-2 negative pregnant women with lesions or asymptomatic shedding at delivery was 94.9%.

The rate of no NH in the case of Caesarean delivery in HSV-2 positive pregnant women with lesions or asymptomatic shedding at delivery was 99.8% (alternative value 99.2%).

The rate of NH in the case of vaginal delivery in HSV-2 positive pregnant women with asymptomatic shedding at delivery was 1% (alternative values 3.6% and 0.4%).

The rate of NH in the case of vaginal delivery in HSV-2 positive pregnant women with lesions at delivery was 4% (alternative value 1%).

The rate of NH in the case of vaginal delivery in HSV-2 negative pregnant women with asymptomatic shedding at delivery was 33%.

The rate of NH in the case of vaginal delivery in HSV-2 negative pregnant women with lesions at delivery was 50%.

Life expectancy was 20 years for severely impaired individuals and 76.40 for non-impaired individuals (as in US life tables). The discounted (at 3%) weighted average life expectancy for all infants with NH using a mix of severity was 22.81 years (undiscounted 55.35) for those treated with antiviral therapy versus 30.10 years (undiscounted 76.4) for an infant without NH.

The utility weights were 0.82, 0.52 and 0.16 for those with mild, moderate and severe impairment, respectively.
Methods used to derive estimates of effectiveness
Some assumptions were made to derive clinical estimates that were not available from the literature, or to define the pattern of care associated with the three interventions examined in the study.

Estimates of effectiveness and key assumptions
The time of testing was 15 weeks of pregnancy.

For seropositive pregnant women, AST started at week 36 and was taken for an average of 28 days. For seropositive partners of seronegative pregnant women, AST started at week 15 for an average duration of 175 days.

Duration of life was 20 years for those who are severely impaired.

The probability that pregnant women with diagnosed genital herpes would take AST from 36 weeks with no testing programme was 25% (alternative value 30%). The probability that a pregnant HSV-2 positive woman or partner was offered and accepted AST with testing programme was 57% (alternative values 30% and 90%). The probability that the partner of a pregnant woman complies with AST was 75% (alternative values 50% and 90%).

The probability that an HSV-2 negative pregnant woman acquires a new HSV-2 infection in the last 8 weeks of pregnancy was 1.32%.

The rate of lesions detected at delivery with no screening programme was 75% (alternative values 65% and 85%).

Measure of benefits used in the economic analysis
The summary benefit measures used were the quality-adjusted life-years (QALYs), life-years (LYs) and cases of NH. All measures were estimated using the decision model approach. Benefits such as QALYs and LYs were discounted at an annual rate of 3%.

Direct costs
The perspective adopted in the study was unclear. Medical care, institutional care and special education costs were considered in the analysis. The health services included were those associated with Caesarean delivery, testing, counselling, antiviral suppression and lifetime treatment for NH. The unit costs were not presented separately from the quantities of resources used. Most of the costs were reported as macro-categories. Resource use was mainly estimated on the basis of authors’ opinions, as the source of the data was not reported. Some costs were estimated from published studies, authors’ assumptions and average wholesale prices. The unit costs for the drugs and for the HSV-2 test were provided. It was unclear whether discounting was used, although it was relevant. The costs were presented using 2003 values. Inflation factors (for the month of June) from the Consumer Product Index medical services component were used, when necessary.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not considered.

Currency
US dollars ($).
Sensitivity analysis
Univariate and multivariate sensitivity analyses were carried out to assess the robustness of the model results to variations in those parameters with the greatest impact on the final results and those where there was the greatest uncertainty about their most likely value in the base-case. The ranges of values were generally derived from the literature, although the authors chose some estimates.

Estimated benefits used in the economic analysis
The number of NH cases in a hypothetical cohort of 100,000 women was 36.4 with no test, 20.7 with test for women only, and 19.6 with test for women and partners.

The number of Caesarean deliveries in a hypothetical cohort of 100,000 women was 22,838 with no test, 22,651 with test for women only, and 22,646 with test for women and partners.

Assuming a mix of severity for those treated with antiviral therapy, the discounted QALYs were 19.67 for infants with NH compared with 30.10 for an infant without NH. However, the number of QALYs and LYs associated with each strategy were not reported.

Cost results
In a hypothetical cohort of 100,000 women, the total costs were $118,135,122 with no test (strategy 1), $121,195,317 with test for women only (strategy 2), and $126,723,665 with test for women and partners (strategy 3). Thus, the incremental cost for testing women only over no test was about $3.1 million ($31 per patient), while the incremental cost for testing both women and partners (with respect to no test) was about $8.6 million.

Synthesis of costs and benefits
Incremental cost-effectiveness ratios and cost-utility ratios were calculated to combine the costs and benefits of the alternative screening strategies.

The incremental cost per case of NH avoided was $194,837 with strategy 2 over strategy 1, $510,505 with strategy 3 over strategy 1, and $4,948,541 with strategy 3 over strategy 2.

The incremental cost per LY gained was $26,727 with strategy 2 over strategy 1, $70,028 with strategy 3 over strategy 1, and $678,812 with strategy 3 over strategy 2.

The incremental cost per QALY gained was $18,680 with strategy 2 over strategy 1, $48,946 with strategy 3 over strategy 1, and $474,453 with strategy 3 over strategy 2.

The results of the sensitivity analysis showed that testing was clearly more cost-effective, with lower costs, greater acceptance and compliance with AST, and greater effectiveness of AST. However, testing was less cost-effective when the probability of lesions or asymptomatic shedding at delivery for women who are seropositive but have not been diagnosed with genital herpes was lower, and when the likelihood that their infants might contract NH during vaginal delivery was lower. In general, the incremental cost per QALY gained for strategy 2 compared with strategy 1 was in the range of $9,712 to $99,585.

Authors' conclusions
Type-specific herpes simplex virus Type 2 (HSV-2) serologic testing of pregnant women was a cost-effective strategy within the assumptions of the decision model. Both the cost per discounted life-year (LY) gained and the cost per discounted quality-adjusted life-year (QALY) gained for the testing programme fell within the ranges generally considered to be cost-effective. However, a strategy of testing and treating partners of seronegative women does not appear to have been a cost-effective option.
CRD COMMENTARY - Selection of comparators
The rationale for the selection of the comparators was clear. The two proposed screening strategies were compared with the current pattern of care in the USA. The two new strategies were accurately described. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from the literature. However, the methods and conduct of the review were not reported. No information on the search and inclusion or exclusion criteria was provided. The number of studies included in the review was reported but, with the exception of a few studies, the primary studies were not described. Thus, it was not possible to assess the validity of the primary studies. The authors also made some assumptions to derive clinical data that were not available from the literature. The issue of uncertainty was extensively addressed in the sensitivity analysis and the most relevant clinical parameters were varied.

Validity of estimate of measure of benefit
The benefit measures used in the analysis were appropriate as they estimated the impact of the interventions on the patients' health. The number of NH cases avoided represents a disease-specific measure, but the use QALYs and LYS allows comparisons with the benefits of other health care interventions. The calculation of QALYs was accurately described, and some information on the source of the utility adjustments was provided. The benefits were discounted using the rate recommended in the USA.

Validity of estimate of costs
The authors stated that a societal perspective was adopted in the study, but the cost analysis was restricted to direct medical costs. In fact, costs relevant to the patient or non-medical institutions were not considered. The authors made some assumptions to derive costs and resource use data. Most of the costs were not presented separately from the quantities of resources used. No statistical analyses were carried out on the costs, but the cost estimates were extensively varied in the sensitivity analysis. The price year was reported, which aids reflation exercises in other time periods. Overall, limited information on the cost analysis was provided.

Other issues
The authors stated that their findings were consistent with those from a published economic evaluation that had shown similar results for the cost-effectiveness analysis. Some comparisons with the estimates of cost-effectiveness of screening programmes for human immunodeficiency virus infection were also made. The issue of the generalisability of the study results to other settings was not explicitly addressed, but the extensive use of sensitivity analyses enhances the external validity of the study. The authors noted also some limitations of their model. For example, the fact that maternal HSV-1 infection was not considered. Moreover, some probability estimates were derived from patient populations slightly different from that considered in the study. The lack of data on long-term outcomes for infants with NH was a further drawback of the model.

Implications of the study
The study results support the use of HSV-2 serologic testing of pregnant women. The authors stated that further research should corroborate the results of the decision model.

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Bibliographic details
Other publications of related interest
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Randolph AG, Washington AE, Prober CG. Cesarean delivery for women presenting with genital herpes lesions. JAMA
1993;270:77-82.

Binkin NJ, Koplan JP. The high cost and low efficacy of weekly viral cultures for pregnant women with recurrent

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