The cost-effectiveness of routine antenatal screening for maternal herpes simplex virus-1 and -2 antibodies

Thung S F, Grobman W A

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 compared three main strategies in pregnant women without a known history of genital herpes simplex virus (HSV):

the current standard of care (no screening for HSV);

antepartum HSV-1 and -2 antibody screening of the pregnant woman and her male partner with appropriate counselling; and

antepartum HSV-1 and -2 antibody screening with appropriate counselling and acyclovir prophylaxis at 36 weeks of gestation in seropositive women. The acyclovir dose was 400 mg, three times daily.

Type of intervention
Screening.

Economic study type
Cost-utility analysis.

Study population
The hypothetical population comprised a cohort of 100,000 pregnant women without a known history of genital HSV.

Setting
The setting was primary care. The economic study was carried out in Illinois, USA.

Dates to which data relate
The studies that provided effectiveness evidence dated from 1991 to 2003. For cost data, the date range was 1993 to 2003. The price year was 2003.

Source of effectiveness data
The evidence was derived from a review or synthesis of completed studies and estimates based on authors' opinions.

Modelling
The authors used a decision tree model to compare the three strategies (the structure of the decision tree was not reported in the paper). Neonatal HSV could be acquired from a primary, non primary, or recurrent maternal genital infection. A primary infection was defined as an infection with either HSV-1 or -2 in an individual who did not have circulating antibodies to either virus. A non primary infection occurred when an individual, in whom antibodies to one
HSV serotype had developed previously, acquired the HSV infection to which she had no circulating antibodies. Recurrent infections resulted from reactivation of the virus in an individual with antibodies to that viral type. The model assumed that in both screening strategies (HSV-1 and -2 antibody screening with or without acyclovir prophylaxis), screening coupled with education and behaviour modification could reduce the risk of acquiring a new HSV infection during pregnancy.

**Outcomes assessed in the review**
The following parameters were used in the model:

- Maternal and paternal serostatus;
- The specificity and sensitivity of the HSV test;
- The seroconversion rate during pregnancy;
- The reduction in seroconversion rate during pregnancy due to counselling;
- The percentage of primary or non primary infections with viral shedding at delivery;
- Recurrent viral shedding at delivery;
- The reduction in recurrent viral shedding caused by acyclovir prophylaxis;
- Symptomatic lesions identified during viral shedding;
- Caesarean delivery with symptomatic or asymptomatic infection;
- Vertical transmission with viral shedding at delivery; and
- The reduction in vertical transmission due to Caesarean delivery.

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

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
No criteria were used to ensure the validity of the primary studies.

**Methods used to judge relevance and validity, and for extracting data**
No methods were used to judge the relevance and the validity of the extracted data.

**Number of primary studies included**
Eighteen studies were included in the review.

**Methods of combining primary studies**
A narrative method was used to combine the primary studies.
Investigation of differences between primary studies
The authors did not investigate possible differences between the primary studies.

Results of the review
The base-case values were as follows.

The maternal serostatus (HSV-1/-2) was 23% for negative/negative, 49% for positive/negative, 11% for negative/positive, and 17% for positive/positive. The paternal serostatus (HSV-1/-2) was 31% for negative/negative, 51% for positive/negative, 5% for negative/positive, and 13% for positive/positive.

The test for HSV-1 had a sensitivity of 95% and a specificity of 96%. The test for HSV-2 had a sensitivity of 98% and a specificity of 97%.

The seroconversion rate during pregnancy was 0.67% for primary infection and 0.07% for non primary infection. For HSV-2, the rate for primary and non primary infections was 2%.

The reduction of seroconversion during pregnancy due to counselling (relative risk) was 0.75% for HSV-1 or HSV-2.

The percentage of primary or non primary infections with viral shedding at delivery was 6% for HSV-1 and 10% for HSV-2.

The recurrent viral shedding at delivery, with seroconversion during pregnancy, was 3.5% for HSV-1 and 7% for HSV-2. The recurrent viral shedding at delivery, with distant seroconversion, was 0.05% for HSV-1 and 1.5% for HSV-2.

The reduction of recurrent viral shedding caused by acyclovir prophylaxis (relative risk) was 0.33 for HSV-1 or HSV-2.

The percentage of symptomatic lesions identified during viral shedding was 10% for no screening and 40% for screening.

The proportion of Caesarean deliveries was 79% with symptomatic infection and 23% with asymptomatic infection.

Vertical transmission with viral shedding at delivery was 50% for HSV-1 or -2 primary; 33% for HSV-1 or -2 non primary; 25% for HSV-1 recurrent; and 0.5% for HSV-2 recurrent. The reduction in vertical transmission due to Caesarean delivery (relative risk) was 0.2% for HSV-1 or HSV -2.

Most parameters included in the model had their corresponding ranges adequately referenced by the authors.

Methods used to derive estimates of effectiveness
This analysis was based on published data and authors’ assumptions.

Estimates of effectiveness and key assumptions
The actual risk of HSV-1 seroconversion that was specifically due to genital disease, rather than oral disease, was unavailable from the published literature and was therefore estimated. The authors used two different viral shedding rate estimates, depending on the temporal proximity of seroconversion to delivery. Although the life span of infected neonates was not well-described in the literature, in order not to bias the model against screening, the authors assigned a life expectancy of 76 years for both healthy individuals and affected neonates.

Measure of benefits used in the economic analysis
The authors used quality-adjusted life-years (QALYs) gained as a measure of benefit. In the base-case analysis, they assigned a utility value of 1 for normal health and mild neurologic deficits, 0.5 for moderate neurologic deficits, 0.1 for severe neurologic deficits, and 0 for death. The QALYs were discounted at a rate of 3%. The number of neonatal
infections prevented and associated neurologic deficits or deaths averted were also assessed.

**Direct costs**
The costs included in the study were screening for HSV-1 and/or HSV-2, counselling, acyclovir supplies, delivery (including elective Caesarean, labour Caesarean and vaginal delivery) and infection. The costs of infection included acute care plus long-term care for neurologic deficits (normal or mild deficit, moderate deficit, severe deficit, and death). The costs were discounted at a rate of 3% and adjusted to 2003 using the medical care component of the Consumer Price Index. The estimations of the quantities and of the total costs were derived using modelling. The resource quantities and the costs were not reported separately. The cost data came from published medical and government literature. The price year was 2003. The cost estimates included in the model had their corresponding ranges adequately referenced by the authors.

**Statistical analysis of costs**
No statistical analysis of the quantities or costs was reported.

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

**Currency**
US dollars ($).

**Sensitivity analysis**
Sensitivity analyses were performed to assess the robustness of the results. A one-way sensitivity analysis was performed to evaluate the impact of changing the probability and cost variables on the cost-effectiveness ratio of HSV antibody screening with counselling and acyclovir prophylaxis.

The possibility of choosing to forego paternal testing and only to intervene on the basis of maternal serologic status was assessed. The reductions in risk were also examined since, in some trials, counselling has failed to result in reductions in sexually transmitted diseases. In addition, because the life span of infected neonates was not well described in the literature, a lifespan range of 50 to 76 years for affected neonates was examined in the sensitivity analysis.

**Estimated benefits used in the economic analysis**
Compared with no screening, the base-case gain per 100,000 pregnancies was 53.24 QALYs with screening and 106.34 QALYs with screening plus prophylaxis. The neonatal infections averted per 100,000 women were 4.70 with screening and 9.39 with screening plus prophylaxis. The neurologic deficits or deaths averted per 100,000 women were 2.01 with screening and 3.8 with screening plus prophylaxis.

**Cost results**
For the base-case, the total cost was $558,103,353 for standard care, $569,788,503 for screening, and $574,690,284 for screening plus prophylaxis.

An incremental analysis was performed. In comparison with no screening, the marginal cost was $11,685,150 for screening and $16,586,931 for screening plus prophylaxis.

**Synthesis of costs and benefits**
The incremental cost-effectiveness ratio for screening versus the standard care strategy (no screening) was unfavourable ($219,513 per QALY gained). The same unfavourable result was obtained for screening plus prophylaxis versus no
screening ($155,988 per QALY gained).

The marginal cost per infection averted was $2,484,980 with screening and $1,765,852 with screening plus prophylaxis. The marginal cost per neurologic deficits or death averted was $5,812,819 with screening and $4,130,297 with screening plus prophylaxis.

The model was robust to all parameters at the ranges that the authors examined. It should be noted that this robustness was demonstrated even when the screening algorithm was changed to eliminate all paternal screening costs, to reflect a strategy in which only maternal screening was performed. This "maternal screening only" strategy had a cost-effectiveness ratio of $120,889.

The model was most sensitive to changes in the vertical transmission rate of recurrent HSV-1 and -2 and the discount rate. Yet, even when the estimates of these variables were changed to the most extreme value that would favour the screening strategy, screening was not cost-effective. For example, lowering the discount rate to 1% improved the cost effectiveness only to $88,093 per QALY gained. Similarly, even if the HSV-2 vertical transmission for recurrent infection was as high as 5%, the screening strategy would remain not cost-effective at $67,401 per QALY gained. As for HSV-1 recurrent genital infection, the highest estimation of vertical transmission (50%) resulted in a cost of $98,346 per QALY gained.

Authors' conclusions
The analysis demonstrated that the incorporation of routine herpes simplex virus (HSV) screening during pregnancy for women without a history of genital HSV infection, to reduce neonatal infection at delivery, would not be cost-effective. Although no strategy in the analysis appears to have been cost-effective, the addition of acyclovir prophylaxis was more cost-effective than screening with counselling alone.

CRD COMMENTARY - Selection of comparators
A justification was given for the comparators used. The no screening strategy is the current standard of care outlined by the American College of Obstetricians and Gynaecologists. You should decide if these strategies represent widely used technologies in your own setting.

Validity of estimate of measure of effectiveness
The authors conducted a review of the literature. There was no indication that it was a systematic review. The authors also made some assumptions that were justified with reference to the medical literature. The methodology for selecting and reviewing the literature used was not reported. Consequently, the authors might have used data from the primary studies selectively. The impact of differences between the studies identified was not considered when estimating effectiveness. To test the robustness of the model, a sensitivity analysis was used to assess the influence of the parameters at the ranges the authors examined.

Validity of estimate of measure of benefit
The authors used QALYs as a measure of benefits. The estimation of utility weights was taken from the literature, and no further detail was provided. The estimation of benefits was modelled through a decision tree. Given the long time horizon (i.e. longer than 2 years), discounting was appropriately used. The authors explored a range of utility values in the sensitivity analysis.

Validity of estimate of costs
The authors reported that the costs were estimated from a health system perspective. As such, all the relevant cost categories appear to have been included. Although all the costs were taken from different sources and years, they were adjusted to year 2003 using the medical care component of the Consumer Price Index and discounted at an annual rate of 3%. The cost estimates were taken from published sources and reported separately from other model parameters, but the resource use quantities were not reported separately. This will limit the reproducibility of the study in other settings.
Statistical analyses of the resource quantities or costs were not conducted (i.e. the costs were treated deterministically). However, the robustness of the estimates used was investigated in a sensitivity analysis.

Other issues
The authors compared their findings with those from other studies and found them, in general, to be concordant. They did not address the issue of generalisability of the results to other settings. The authors acknowledged some limitations. For example, as in any model, the data were limited, owing to the quality of the estimates of neonatal infection rates and medical costs. Also, the indirect or social costs of routine HSV screening and intervention were not captured. The psychological or financial impact on a family that cares for a neurologically impaired child, the social costs of informing a couple that they have been exposed to HSV-2, a known sexually transmitted disease, and the anxiety that could result during the pregnancy were also unknown and were not included.

Implications of the study
Although screening with counselling and screening with counselling plus acyclovir prophylaxis might not be cost-effective for the population at large, the authors stated they could not claim that these strategies should never be offered. For them, every woman must be considered individually. However, they believed that this analysis demonstrated that the incorporation of routine HSV-1 and -2 antibody tests during antepartum care for women without a history of genital HSV infection is not a cost-effective intervention and remains unwarranted.

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