Acyclovir prophylaxis to prevent herpes simplex virus recurrence at delivery: a systematic review


CRD summary
This review assessed prophylactic acyclovir for pregnant women with genital herpes simplex virus (HSV) near term. The authors concluded that acyclovir at 36 weeks' gestation reduces clinical HSV recurrence at delivery, Caesarean section for recurrent genital herpes and shedding of HSV at delivery. This was a well-conducted and clearly presented review. The authors' conclusions are likely to be reliable.

Authors' objectives
To assess the effects of prophylactic acyclovir administered to pregnant women with genital herpes simplex virus (HSV) near term on HSV recurrence at delivery.

Searching
MEDLINE (from 1966 to March 2003), LILACS and EMBASE were searched. Also searched were conference proceedings available online or in published format, and abstracts of the following forums: Society for Maternal-Fetal Medicine (1966 to 2003), Infectious Diseases Society for Obstetrics and Gynecology (1966 to 2002), and the Society for Gynecological Investigation (1996 to 2003). Bibliographies of relevant studies were reviewed. The register of controlled trials in perinatal medicine compiled by the National Perinatal Epidemiology Unit of Oxford University was also searched. No language restrictions were applied to the searches. Only studies reported in full publications or as abstracts in English, French, Spanish, or German were included. For studies published in multiple reports, only the report containing the most information was included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies of prophylactic acyclovir were eligible for inclusion. In the included studies, acyclovir was given at a dose of 200 mg four times daily, or 400 mg three times daily. Treatment was started at 36 weeks' gestation in all of the included studies.

Participants included in the review
Studies of pregnant women with HSV were eligible for inclusion. The included studies were of women with recurrent HSV, a first episode of HSV, and any type of HSV. In the studies, HSV was diagnosed clinically using culture or type-specific serology, or combinations of these methods.

Outcomes assessed in the review
Studies were included if they presented adequate data to calculate summary odds ratios (ORs). The review assessed recurrent genital herpes at delivery, Caesarean deliveries performed for clinical HSV recurrence or prodromal symptoms, and HSV detection at delivery. The clinical and virological recurrence of HSV was assessed.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Studies were assessed for blinding, the adequacy of allocation concealment, whether sample size estimates were
provided, and the use of intention-to-treat analysis. Three reviewers independently assessed validity.

**Data extraction**
Three reviewers independently extracted the data using a standardised form and resolved any disagreements through consensus. The extracted data included treatment regimen, gestational age at start of treatment, diagnosis of HSV infection, definition of first episode and recurrent HSV infection, and results. The data were extracted on an intention-to-treat basis. Where required, the authors were contacted for further outcomes data.

**Methods of synthesis**
How were the studies combined?
The studies were combined in a meta-analysis. Pooled ORs and 95% confidence intervals (CIs) were calculated using a fixed-effect model (Peto) in the absence of statistical heterogeneity, and a random-effects model in its presence. In the meta-analysis, 0.5 was added to any cells with zero events. The possibility of publication bias was explored using a funnel plot.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared statistic. A sensitivity analysis was conducted by analysing the studies according to the adequacy of blinding, type of HSV disease (first episode versus studies that included women with recurrent disease) and dose of acyclovir (800 mg/day versus 1,200 mg/day).

**Results of the review**
Five RCTs (799 women) were included.

Four RCTs reported an estimation of sample size, but none reached the minimum estimated sample size. One RCT did not report adequate allocation concealment. Four RCTs reported analysis on an intention-to-treat basis.

Acyclovir significantly reduced clinical HSV recurrence at the time of delivery (4% versus 15% for controls). The OR was 0.25 (95% CI: 0.15, 0.40). No statistically significant heterogeneity was detected (P=0.19).

Acyclovir significantly reduced Caesarean section delivery for clinical HSV recurrence (4% versus 14.6% for controls). The OR (random-effects model) was 0.30 (95% CI: 0.13, 0.67). Statistically significant heterogeneity was detected (P=0.02). Acyclovir also significantly reduced Caesarean section delivery for any indication (OR 0.61, 95% CI: 0.43, 0.86). No statistically significant heterogeneity was detected (P=0.86).

Acyclovir significantly reduced the detection of HSV at delivery using viral culture (0% versus 5% for controls). The OR (4 RCTs) was 0.11 (95% CI: 0.04, 0.31). No statistically significant heterogeneity was detected (P=0.99).

Acyclovir significantly reduced asymptomatic shedding at delivery. The OR (4 RCTs) was 0.09 (95% CI: 0.02, 0.39). No statistically significant heterogeneity was detected (P=0.94).

Similar results were obtained for clinical recurrence at delivery when analysing only studies with adequate blinding. The results were similar for both dosing regimens of acyclovir and by type of disease. These results were reported.

None of the studies reported any cases of neonatal herpes.

The funnel plot suggested a low possibility of publication bias.

**Authors' conclusions**
Prophylactic acyclovir beginning at 36 weeks' gestation reduced clinical HSV recurrence at delivery, Caesarean section for recurrent genital herpes, and shedding of HSV at delivery.
**CRD commentary**
The review question was clear in terms of the study design, participants, intervention and outcomes. Several relevant sources were searched, the search terms were stated, and studies in any one of four languages were eligible. Unpublished studies were excluded, thus raising the possibility of publication bias. The methods used to select the studies and assess validity were not described, so it is not known whether efforts were made to reduce errors and bias. Methods to minimise bias were used in the data extraction process.

The data were appropriately combined in a meta-analysis, statistical heterogeneity was assessed, and sensitivity analyses were carried out. There was no exploration or discussion of potential reasons for the significant heterogeneity detected for the analysis of Caesarean section rates. This means that, although the direction of effect was consistent among the studies, the size of the effect on Caesarean section rates is uncertain. The evidence presented appears to support the authors' conclusions.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The authors stated that ongoing trials of other prophylactic antiviral regimens should assess rates of clinical recurrence, asymptomatic shedding and neonatal HSV. Studies should also assess the effects of treatments on exposed neonates and evaluate renal, hepatic and haematological function at follow-up. The authors also stated that research on interventions to reduce genital HSV is required.

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