**OBJECTIVE:** To estimate whether serotyping women with a history of genital herpes simplex virus (HSV) and an outbreak during the third trimester of pregnancy is cost effective compared with no serotyping.

**METHODS:** We designed a decision-analytic model using TreeAge Pro software to assess an approach of routine HSV serotyping in a theoretical cohort of 63,582 women (an estimate of the number of women in the United States with a history of genital HSV and an outbreak during the third trimester of pregnancy). Outcomes included mild, moderate, and severe neonatal HSV, neonatal death, costs, and quality-adjusted lifeyears (QALYs) for both the woman and neonate. Probabilities, utilities, and costs were derived from the literature, and we used a willingness-to-pay threshold of \$100,000 per QALY. Sensitivity analyses were performed to assess the robustness of the results.

**RESULTS:** In our theoretical cohort, HSV serology screening resulted in 519, 8, and 15 cases of mild, moderate, and severe neonatal HSV, whereas no serology screening resulted in 745, 65, and 85 cases, respectively. Thus, HSV serology screening led to 226, 57, and 70 fewer cases of mild, moderate, and severe neonatal HSV, respectively, as well as 91 fewer neonatal deaths. Additionally, serology screening saved \$61 million and gained 7,900 QALYs, making it a dominant strategy. Univariate sensitivity analysis demonstrated that serology screening was cost effective until the chance of progression from neonatal HSV infection to disease despite empiric antiviral treatment was greater than 23%.

**CONCLUSION:** Serology screening in pregnant women with an outbreak in the third trimester of pregnancy and a history of genital HSV resulted in improved outcomes and decreased costs.