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Acyclovir suppression to prevent recurrent genital herpes at delivery

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Objective: To determine if suppressive acyclovir near term decreased the frequency of clinical recurrences at delivery in women with recurrent genital herpes simplex virus (HSV) infection.

Methods: We conducted a prospective, double-blind, randomized trial in 234 women with recurrent genital herpes. Women with genital infection of any frequency were enrolled. Patients received either suppressive oral acyclovir 400 mg three times daily or an identical placebo after 36 weeks' gestation. Clinical lesions were identified, and HSV cultures were obtained at delivery. The frequencies of clinical and subclinical HSV recurrences at delivery were evaluated.

Results: Six percent of patients treated with acyclovir, and 14% of patients treated with placebo had clinical HSV at delivery ($p = 0.046$). No patients in the acyclovir group had positive HSV cultures, compared with 6% of placebo-treated patients ($p = 0.029$). There was no significant difference in subclinical HSV shedding in the acyclovir group (0%) compared with the placebo-treated group (3%) ($p = 0.102$).

Conclusions: Suppressive acyclovir therapy significantly decreased the incidence of clinical genital herpes and the overall incidence of HSV excretion at delivery in patients with previous herpes infection.

Key words: ANTIVIRAL AGENTS; PREGNANCY COMPLICATIONS, INFECTIOUS; HERPES GENITALIS; HERPES SIMPLEX; CESAREAN DELIVERY

It is estimated that 5% of the general population has a known history of genital herpes[1]. This creates a large population of women known to be at risk for transmitting herpes simplex virus (HSV) to their infants during delivery, should they have a peripartum recurrence. To avoid intrapartum HSV exposure and neonatal infection, it is currently recommended that pregnant women with visible genital herpes lesions or prodromal symptoms at the time of labor have a Cesarean delivery. Gravidas without visible lesions or prodromal symptoms should be allowed to continue in labor because they have a low risk of neonatal HSV transmission[1,2]. Using these guidelines, it is estimated that one poor neonatal outcome from HSV infection is averted for every 1580 Cesarean deliveries performed for maternal clinical HSV recurrences[3] (at a cost of US$2.5 million).

Suppressive acyclovir therapy decreases the frequency of clinical and subclinical HSV reactivation in non-pregnant adults[4]. A typical suppressive dose in the non-pregnant adult is 400 mg orally, twice per day[5]. However, pharmacokinetic studies in term gravidas have shown that 400 mg orally, three times daily (t.i.d.) may be necessary to achieve similar therapeutic serum levels[6]. We have

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previously shown that suppressive acyclovir therapy, given from 36 weeks' gestation until delivery, is effective in preventing recurrences of genital herpes at delivery in patients who experienced their first genital herpes episode in that pregnancy[7]. However, the efficacy and safety of such therapy for patients with genital herpes predating their pregnancy is unknown. The purpose of this study was to determine if acyclovir suppressive therapy, administered in the last few weeks of pregnancy, would decrease the frequency of symptomatic genital HSV at delivery in women who have a history of recurrent genital herpes.

MATERIALS AND METHODS

Eligible patients included any gravida with genital herpes diagnosed by a viral culture positive for HSV or by the patient's recollection of a health care provider's clinical diagnosis before the current pregnancy. Gravidas were eligible for enrollment with any frequency of recurrences. Herpes simplex viral serology was not performed. These criteria were selected to represent those used in typical contemporary clinical practice.

Exclusion criteria included serum creatinine greater than 1.5 mg/dl, immunosuppressive diseases (e.g., HIV infection), a known requirement for Cesarean delivery (e.g. previous Cesarean with a classical uterine incision), enrollment in another study protocol, a gestational age of greater than 36 weeks upon identification, delivery before 36 weeks' gestation or previous acyclovir intolerance. A patient was considered to be non-compliant if she had not taken any study medication on each of the seven days immediately prior to delivery. All subjects with known outcomes were included in an intent-to-treat analysis.

Patients were recruited from the prenatal clinics at Parkland Health and Hospital System and St. Paul Medical Center. Both of these clinic systems serve a young, indigent population with a high incidence of sexually transmitted diseases. Informed consent was obtained from eligible patients by 36 completed weeks of gestation. At 36 weeks estimated gestational age, a schedule generated from a random number table was consulted, and women were assigned to receive either acyclovir 400 mg (GlaxoSmithKline, Research Triangle Park, NC) or an identical-appearing placebo, orally, t.i.d until delivery. The acyclovir and placebo were dispensed in coded bottles, and the patients and their physicians were blinded to the study assignment. An individual not involved with patient care maintained the randomization list and assigned the study drug group.

Hypothesizing a symptomatic genital herpes recurrence rate at delivery of 13%[8], a 50% decrease in recurrences at delivery in the treated group, and an 80% power, a sample size of 326 patients in each group (acyclovir and placebo) was projected. The Food and Drug Administration granted an Investigational Drug Number for this protocol; and the investigational review boards of the University of Texas Southwestern Medical Center, Parkland Health and Hospital System and St. Paul Medical Center granted approval for the study.

The women were evaluated weekly after 36 weeks' gestation and were questioned at each visit about genital lesions, prodromal symptoms, compliance and side effects from the treatment. Prodromal symptoms were defined as tingling, itching, or other sensations that the patient typically related to the onset of her herpes recurrence. Pill counts were performed at return visits and at delivery, when possible; and we also relied on reported compliance. Non-compliance was defined as no study medication for seven days prior to delivery. An examination for genital HSV lesions was performed at each visit. Herpes cultures were obtained only if the patient described prodromal symptoms or if a lesion was identified. The collection, handling and culture technique has been described previously[7,9]. Upon presentation for delivery, the patients were examined for genital lesions and questioned regarding prodromal symptoms. For asymptomatic patients, a combined herpes culture of the usual lesion site and cervix was obtained to detect asymptomatic viral shedding. For symptomatic women, any visible genital or cervical lesions were also cultured for HSV. Obstetric residents or nurse practitioners that had been instructed in proper viral culture collection technique collected the samples from patients upon their admission to the Labor and Delivery unit. Study medications were not continued intrapartum. Patients were delivered by Cesarean section if prodromal symptoms or lesions suspicious

for genital herpes were present, regardless of the length of time the amniotic membranes had been ruptured. They were allowed to labor if prodromal symptoms and lesions were absent.

The pediatricians were informed of the mother's participation in the study, and a physical exam was performed upon the infant's admission to the newborn nursery. Neonatal HSV cultures were taken from the conjunctiva, oropharynx and rectum 24–48 hours after delivery; the specimens were combined in one culture. The infants were observed for the duration of their routine neonatal stay for clinical evidence of acyclovir toxicity (abnormal renal, liver or central nervous system function) and HSV infection. Prophylactic acyclovir therapy was not administered unless the infant was thought to have been exposed to an active herpes lesion. In that case, the decision to initiate treatment was left to the discretion of the attending pediatrician. Mothers were instructed to contact the investigators for any problems in the first month after discharge, and the infants' medical records were reviewed at least one month after delivery.

Statistical analysis

Statistical analysis included chi-square and two-tailed Fisher exact tests to evaluate differences between the acyclovir and placebo treatment groups. Odds ratios were calculated with 95% exact confidence limits. A p value less than 0.05 was considered statistically significant. The primary outcome measured was the frequency of clinical genital herpes recurrences at delivery. Secondary outcomes included the frequency of asymptomatic viral shedding, the frequency of total viral shedding, and the frequency of Cesarean delivery for recurrent herpes between the two groups. All comparisons were done using an intent-to-treat format. Outcomes were not compared by frequency of recurrences, for there were too few women with six or more recurrences annually.

RESULTS

Between February 1, 1992 and January 31, 1998, 234 women with a history of genital herpes were identified and agreed to participate in the study. Because only 36% of the anticipated sample size was enrolled after six years, we felt that an additional ten years necessary to complete enrollment was not feasible. Further recruitment was terminated at that time, but patients who had already enrolled were allowed to complete the study.

Selected maternal and neonatal characteristics are presented in Table 1. One hundred sixteen women were randomized to acyclovir and 118 were randomized to placebo. Twenty-one patients in each group did not complete the study. Outcome information was available for all but three of these patients (all in the placebo group) who were lost to follow-up. Differences between the acyclovir and placebo groups for the various analyses are presented in Table 2. Two hundred thirty-one patients with known outcomes were considered in an intent-to-treat analysis; 116 were assigned to acyclovir and 115 to placebo. Six percent (7/116) of the acyclovir-treated patients had clinically evident genital herpes at the time of delivery, compared with 14% (16/115) of the placebo treated patients ($p = 0.046$). This was a 57% relative decrease in the incidence of clinical reactivations of genital herpes at the time of delivery. However, the difference in frequency in Cesarean delivery between the two groups was not significant (Table 3).

Table 1 Maternal and neonatal characteristics

Characteristics	*Acyclovir* ($n = 116$)	*Placebo* ($n = 115$)
Ethnicity		
Black	40%	47%
White	31%	31%
Hispanic	28%	20%
Other	1%	1%
Age	24.8	24
Parity*	0	0
Outbreaks/year	2.6	2.6
Outbreaks during study	1.1	1.4
Gestational age at delivery	39.4 weeks	39.4 weeks
Birthweight	3352 g	3401 g
Five minute Apgar*	9	9
Cord pH	7.28	7.26

Data presented as percentage, mean, or median* of sample

Table 2 Differences between acyclovir and placebo groups for various outcome measures, at presentation for delivery

Outcome measure at	*Acyclovir*	*Placebo*	p *value*	*OR* [95% CI]
Clinical HSV recurrence	7/116 (6%)	16/115 (14%)	0.046[a]	0.40 [0.13, 1.08]
Cesarean for HSV	8/116 (7%)	14/115 (12%)	0.172[a]	0.53 [0.19, 1.44]
HSV recovery from lesions[b]	0/5 (0%)	3/16 (19%)	0.549[c]	0 [0, 8.32]
Asymptomatic HSV shedding[b]	0/97 (0%)	3/86 (3%)	0.102[c]	0 [0, 2.13]
Total HSV viral excretion[b]	0/102 (0%)	6/102 (6%)	0.029[c]	0 [0, 0.83]

OR, odds ratio; CL, confidence limits; HSV, herpes simplex virus; [a]Chi-square analysis, intent-to-treat; [b]*n* is less than total number of patients since some patients did not have cultures obtained; [c]Fisher exact test, 2-tailed

Table 3 Indications for Cesarean delivery

Indication	*Acyclovir* (*n* = 116)	*Placebo* (*n* = 115)
Repeat	4	4
Failure to progress	10	10
Malpresentation	3	4
Fetal distress	2	3
Other	2	0
HSV	8[a]	14[b]
TOTAL	29 (25%)	35 (30%)

[a]In a breach of the study protocol, one patient had a Cesarean delivery for genital herpes without a clinical recurrence at delivery; [b]Two patients with genital lesions inadvertently delivered vaginally due to rapid delivery and protocol error

There was no significant difference between the two groups in the incidence of asymptomatic (subclinical) HSV shedding at the time of delivery. There was no significant difference between the treatment groups in the incidence of viral recovery from clinically apparent lesions. However, when the total viral recovery (subclinical shedding + shedding from clinical lesions) was compared, there was a significant difference between the treatment groups. None (0/102) of the acyclovir-treated patients, but 6% (6/102) placebo-treated patients had virus recovered from the genital tract at presentation for delivery ($p = 0.029$).

One infant in the placebo group received prophylactic acyclovir therapy until his cultures returned negative. Although the mother had a Cesarean delivery, she had virus recovered from lesions on her cervix and labia, and the infant had transiently elevated liver transaminases after birth. Ultimately he did well. Two other infants from the placebo group whose mothers had genital lesions but delivered vaginally were observed without treatment. Their HSV cultures returned negative, and neither developed any signs of neonatal infection. No infant in either the acyclovir or placebo group had clinical evidence of HSV infection, although one infant born vaginally to a mother who was not compliant with acyclovir treatment did have a transiently positive HSV culture. The mother's cultures taken at admission for labor were negative. The infant was observed without treatment, and subsequent HSV cultures were negative. No other infants experienced any clinically apparent neurologic, hepatic or renal complications or other adverse effects attributable to acyclovir during the neonatal period.

DISCUSSION

In an effort to prevent intrapartum HSV transmission, obstetricians generally resort to Cesarean delivery when a patient presents for delivery with recurrent genital herpes lesions or prodromal symptoms. Under current guidelines, a vaginal delivery is appropriate in the absence of these findings[1,2]. Daily acyclovir therapy suppresses recurrent genital HSV outbreaks in the non-pregnant adult[4], and it has been suggested that this treatment be considered as a means to prevent herpes reactivation at delivery[2].

Our study demonstrated that pregnant women with a history of recurrent genital herpes might decrease their risk of clinical reactivation at the time of delivery by more than 50% by using suppressive acyclovir therapy. These findings are similar to those reported by Brocklehurst and colleagues[10]. These investigators reported a clinically important reduction in the incidence of herpes lesions present at the time of delivery, but

terminated the study early due to enrollment difficulties. Unfortunately, the Brocklehurst study did not have adequate power to rule out a significant difference.

The significant reduction in clinical herpes recurrences for our acyclovir treated patients did not translate into a similar significant reduction in Cesarean deliveries. Possible explanations include: the decision to perform a Cesarean delivery based only on a history of genital herpes (in spite of the current ACOG recommendations)[2], inadvertent vaginal delivery, and other indications for Cesarean (such as breech presentation) in addition to the presence of a herpes lesion (Table 3).

A recent cost-benefit analysis was performed for the use of acyclovir suppression in the last several weeks of pregnancy. The authors concluded that suppressive therapy would cost less, would result in decreased maternal morbidity and mortality, and would result in fewer cases of neonatal herpes than deferring acyclovir treatment and resorting to Cesarean delivery for clinical reactivations[11].

A theoretical concern is whether symptomatic recurrences would be converted to asymptomatic shedding episodes by suppressive treatment, thus potentially increasing an infant's perinatal exposure to HSV through a vaginal delivery[12]. The reported incidence of asymptomatic HSV shedding at any given time in pregnant women with genital herpes is about 1–2%[13–15]. Wald and colleagues[16] reported that acyclovir suppression decreased asymptomatic shedding by 96% in non-pregnant patients, but this reduction has not yet been confirmed in pregnant women. We found a significant decrease in clinical genital lesions (14% versus 6%), but no difference in subclinical shedding (3% versus 0%) in the group treated with suppressive acyclovir therapy. There was no evidence that clinical lesions were replaced by asymptomatic shedding.

In fact, acyclovir suppressive therapy significantly decreased the total incidence of virus recovered at presentation for delivery. This has important implications in that the primary time of fetal exposure is during the intrapartum period, regardless of whether the infant is delivered vaginally or by Cesarean section. The decreased incidence of viral shedding may decrease the potential for intrapartum HSV exposure.

On short-term follow-up, there were no apparent adverse effects on any of the neonates who had prenatal exposure to acyclovir, 1200 mg daily, at term. Data from the Acyclovir in Pregnancy Registry do not suggest adverse outcomes attributable to acyclovir in over 1200 prenatal exposures, regardless of gestational age[17]. Additional anecdotal evidence of acyclovir's safety is provided indirectly through reported pediatric clinical experience. Both term and preterm infants treated daily with intravenous acyclovir tolerate the drug well[18,19]. Furthermore, the fetal serum levels in gravidas taking 1200 mg acyclovir daily have been reported to be much lower than the acyclovir levels achieved during neonatal parenteral treatment[6,18,19]. However, clinical evaluation is relatively insensitive to identify sequelae from drug treatment, and we cannot conclude that prenatal suppressive acyclovir therapy is completely safe for the fetus. This study was not designed or powered to specifically test for newborn safety. Further evaluation of short- and long-term neonatal outcomes is necessary. In particular, this should include the evaluation of the impact of maternal acyclovir suppression on the fetal and neonatal kidney.

There are some limitations to our trial. First, we did not discriminate between HSV-1 and HSV-2 recurrent genital infections. Since HSV-1 genital infection tends to reactivate less frequently than HSV-2[20], it is possible that the lower frequency of clinical reactivation in the acyclovir treated patients was due to an over-representation of HSV-1-infected patients in the acyclovir group. However, randomization of the patients should have resulted in similar numbers of women with each type of infection in each treatment group. In fact, the mean annual incidence of clinical herpes reactivations prior to pregnancy was the same in each group (Table 1).

Another limitation is the lack of culture-proved diagnoses in all patients considered eligible for participation. However, the practicing clinician often has only the history of the patient to rely on when making a decision regarding management of herpes in pregnancy. Ninety percent of adults with a clinical picture and history compatible with first-episode genital herpes had positive cultures in a recent series[21]. It is possible that some of these

patients were misdiagnosed and did not actually have genital herpes. Randomization of the patients should have resulted in similar numbers of misdiagnosed patients in each treatment group.

The main limitation is that our enrollment was terminated before our planned sample size was reached. It is possible that early termination introduced bias. However, the number of patients enrolled is over twice the size of the enrollment in each of the only other two randomized clinical trials of acyclovir in late pregnancy[10,22]. In addition, one of these trials was also halted early due to low enrollment[10].

In summary, acyclovir suppression in the last several weeks of pregnancy significantly reduced the incidence of clinically evident genital herpes as well as the overall viral excretion rate at the time of delivery in patients with previous herpes infection. We did not observe any short term, adverse effects of treatment on the fetus or neonate; however, further investigation is needed to determine the safety of antenatal acyclovir exposure.

REFERENCES

1. Prober CG, Corey L, Brown ZA, *et al.* The management of pregnancies complicated by genital infections with herpes simplex virus. *Clin Infect Dis* 1992;15:1031–8
2. American College of Obstetricians and Gynecologists. 1999. *Management of herpes in pregnancy.* ACOG Practice Bulletin Washington, D.C. 1999;8
3. Randolph AG, Washington AE, Prober CG. Cesarean delivery for women presenting with genital herpes lesions. *J Am Med Assoc* 1993;270: 77–82
4. Wald A, Corey L, Cone R, *et al.* Frequent genital herpes simplex virus 2 shedding in immunocompetent women: effect of acyclovir treatment. *J Clin Invest* 1997;99:1092–7
5. Centers for Disease Control and Prevention. 1998 Guidelines for treatment of sexually transmitted diseases. *MMWR* 1998;47(RR-1):20–6
6. Frenkel LM, Brown ZA, Bryson YJ, *et al.* Pharmacokinetics of acyclovir in the term human pregnancy and neonate. *Am J Obstet Gynecol* 1991; 164:569–76
7. Scott LL, Sanchez PJ, Jackson GL, *et al.* Acyclovir suppression to prevent Cesarean delivery after first-episode genital herpes. *Obstet Gynecol* 1996;87: 69–73
8. Brown ZA, Vontver LA, Benedetti J, *et al.* Genital herpes in pregnancy: risk factors associated with recurrences and asymptomatic viral shedding. *Am J Obstet Gynecol* 1985;153:24–30
9. Hankins GDV, Cunningham FG, Luby JP, *et al.* Asymptomatic genital excretion of herpes simplex virus during early labor. *Am J Obstet Gynecol* 1984; 150:100–1
10. Brocklehurst P, Kinghorn G, Carney O, *et al.* A randomised placebo controlled trial of suppressive acyclovir in late pregnancy in women with recurrent genital herpes infection. *Br J Obstet Gynaecol* 1998;105:275–80
11. Randolph AG, Hartshorn RM, Washington AE. Acyclovir prophylaxis in late pregnancy to prevent neonatal herpes: a cost-effectiveness analysis. *Obstet Gynecol* 1996;88:603–10
12. Brown ZA, Watts DH. Antiviral therapy in pregnancy. *Clin Obstet Gynecol* 1990;33:276–89
13. Arvin AM, Hensleigh PA, Prober CG, *et al.* Failure of antepartum maternal cultures to predict the infant's risk of exposure to herpes simplex virus at delivery. *N Engl J Med* 1986;315:796–800
14. Wittek AE, Yeager AS, Au DS, Hensleigh PA. Asymptomatic shedding of herpes simplex virus from the cervix and lesion site during pregnancy. Correlation of antepartum shedding with shedding at delivery. *Am J Dis Child* 1984;138:439–42
15. Prober CG. Herpetic vaginitis in 1993. *Clin Obstet Gynecol* 1993;36:177–87
16. Wald A, Zeh J, Barnum G, *et al.* Suppression of subclinical shedding of herpes simplex virus type 2 with acyclovir. *Ann Intern Med* 1996;124:8–15
17. Reiff-Eldridge R, Heffner CR, Ephross SA, *et al.* Monitoring pregnancy outcomes after prenatal drug exposure through prospective pregnancy registries: a pharmaceutical company commitment. *Am J Obstet Gynecol* 2000;182:159–63
18. Hintz M, Connor JD, Spector SA, *et al.* Neonatal acyclovir pharmacokinetics in patients with herpes virus infections. *Am J Med* 1982;73:210–14
19. Yeager AS. Use of acyclovir in premature and term neonates. *Am J Med* 1982;73:205–9

20. Benedetti J, Corey L, Ashley R. Recurrence rates in genital herpes after symptomatic first-episode infection. *Ann Intern Med* 1994;121:847–54
21. Löwhagen G-B, Tunbäck P, Andersson K, *et al.* First episodes of genital herpes in a Swedish STD population: a study of epidemiology and transmission by the use of herpes simplex virus typing and specific serology. *Sex Transm Inf* 2000; 76:179–82
22. Stray-Pedersen B. Acyclovir in late pregnancy to prevent neonatal herpes simplex. *Lancet* 1990;336: 756

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