Uses and Safety of Acyclovir in Pregnancy

John G. Spangler, MD, MPH; Julienne K. Kirk, PharmD; and Mark P. Knudson, MD, MSPH
Winston-Salem, North Carolina

Acyclovir, an antiviral nucleoside analogue, is a widely used agent highly specific for herpes simplex and varicella-zoster viruses. Unintended exposure to acyclovir early in pregnancy, which is not uncommon, may cause excessive maternal and physician anxiety. This drug has not been studied prospectively in large numbers of pregnant women and lacks the Food and Drug Administration's approval for gestational use unless benefits clearly outweigh potential fetal harm. However, data published since acyclovir became available do not indicate increased adverse effects related to its use in pregnancy, especially if prescribed in selected situations, such as disseminated primary herpes simplex infections or maternal varicella pneumonia. This article reports the impact of inadvertent acyclovir exposure on a woman during the first trimester of pregnancy and reviews the literature on acyclovir's pharmacology, safety profile, and potential uses during pregnancy.

Key words. Acyclovir; pregnancy trimester, first; herpes simplex; herpes genitalis; varicella-zoster virus.
(*J Fam Pract 1994; 38:186-191*)

Acyclovir is a widely used antiviral agent of low toxicity available in oral and intravenous forms and used in the United States mainly for suppression of recurrent genital herpes. Up to 50% of users are women of child-bearing age,[1] making unsuspected fetal exposure during the first trimester of pregnancy a common occurrence and increasing the prospect of maternal or physician anxiety. Although the drug has not been approved by the Food and Drug Administration (FDA) for use during pregnancy, the literature cites several situations in which it might have therapeutic value. The purpose of this paper is to present a case illustrating the emotional impact of exposure to acyclovir during the first trimester, to review available data on the drug's pharmacology and safety during pregnancy, and to discuss situations in which its use during pregnancy appears warranted.

Submitted, revised, October 19, 1993.

From the Department of Family and Community Medicine, Bowman Gray School of Medicine of Wake Forest University. Requests for reprints should be addressed to John G. Spangler, MD, MPH, The Department of Family and Community Medicine, Bowman Gray School of Medicine of Wake Forest University, Medical Center Boulevard, Winston-Salem, NC 27157–1084.

ISSN 0094-3509

Case Report

A 29-year-old G_3P_1 white woman came to our clinic for pregnancy testing. Her most recent menstrual period had been 5 weeks earlier. A positive pregnancy test and an initial examination confirmed a pregnancy of 5 weeks' gestation.

The patient, who had a history of recurrent lingual herpes simplex infections, developed pain and burning on the right lateral aspect of her tongue, typical of her herpetic prodrome 10 days prior to the visit. She initiated treatment with acyclovir 200 mg orally five times daily, which she continued until she became aware of missing a menstrual period, at which time she discontinued taking the acyclovir.

The patient's pregnancy was subsequently complicated by an appendectomy performed at 8 weeks' gestation and a low maternal α-fetoprotein test. She refused amniocentesis. An ultrasound at 17 weeks' gestation was unremarkable for developmental abnormalities, but the early exposure to acyclovir caused the patient marked emotional anxiety regarding the health and viability of the fetus. She was enrolled in the Acyclovir in Pregnancy Registry, a program made available by the manufacturer (Burroughs Wellcome Company) to provide information to patients so that they can make informed choices. At 40 weeks' gestation, she gave birth to a healthy female

infant. Two years of follow-up have revealed no abnormalities of growth or development.

Discussion

Acyclovir, a synthetic purine nucleoside analogue introduced in 1982, is the first antiviral agent to possess broad activity against the two types of herpes simplex virus, HSV-1 and HSV-2, and varicella-zoster virus (VZV). Acyclovir is a highly selective agent for the herpes viruses with low toxicity toward the host cell: it inhibits the replication of HSV-1 and HSV-2 but cannot eradicate the latent viral reservoir. This agent has proven to be the most effective and least toxic antiviral agent available for HSV infections.

Pharmacokinetics in Pregnancy

Acyclovir is cleared primarily by the renal route through glomerular filtration and tubular secretion. Absorption of oral acyclovir from the gastrointestinal tract is variable and incomplete with an estimated bioavailability of 15% to 30%, probably caused by a saturable absorption process in which the drug's bioavailability decreases with increasing doses.[2] The average serum half-life used in obstetrics and gynecology is between 2.1 and 3.5 hours.[3] The 50% inhibitory dose for HSV-1 and HSV-2 is 0.1 to 3 μmol/L and for VZV is 3 to 4 μmol/L.[2]

Acyclovir is known to cross the placenta to the fetus. Frenkel et al[4] reported the specific pharmacokinetics of acyclovir in pregnant patients with recurrent HSV receiving either 200 or 400 mg of acyclovir orally every 8 hours from 38 weeks' gestation until delivery. Doses of 200 mg and 400 mg produced mean peak maternal serum concentrations of 1.7 ± 0.6 μmol/L and 2.3 ± 1.0 μmol/L, respectively. Amniotic fluid levels were 2 to 8 times higher than those in maternal plasma, and maternal-to-cord ratios at delivery were between 1.07 and 1.90 μmol/L. Additional trough steady-state acyclovir concentrations for 200 mg and 400 mg doses were reported as 0.7 ± 0.3 and 0.8 ± 0.6 μmol/L, respectively; peak concentrations were 1.9 ± 1.0 and 3.3 ± 1.0 μmol/L, respectively.

Kingsley[5] reported data on 116 pregnant patients who were exposed to acyclovir in the first, second, and third trimesters. In 18 of the 116 neonates, the concentrations of acyclovir in cord blood ranged from <0.5 to 1.23 μmol/L, and 14 samples of amniotic fluid contained between 0.5 and 5.58 μmol/L of acyclovir. In one study, five pregnant patients at term who received acyclovir 200 mg orally every 8 hours had peak maternal plasma concentrations of 2.5 μmol/L approximately 1.5 hours after the dose.[6] In the same report, the drug was noted to be highly concentrated in amniotic fluid and gastric aspirate but not in fetal blood.

In comparison to healthy nonpregnant patients receiving acyclovir, mean peak plasma concentrations following 200 mg orally in pregnant patients are lower[7] and usually occurred within 1.5 to 2.5 hours following administration. Possible reasons for differences in peak concentrations found between pregnant and nonpregnant individuals include an increased volume of distribution and changes in renal clearance of the drug during pregnancy.

Teratogenicity

As an FDA category "C" drug, human data on acyclovir are incomplete, but potential benefits of drugs in this category may justify potential risks. Although no adequate and well-controlled studies have been conducted in pregnant women using acyclovir, it has not proved to be teratogenic in laboratory animals. Data among pregnant rabbits and rats given subcutaneous injections of 15, 25, and 50 mg/kg/d of acyclovir showed neither embryotoxicity nor increased risk of fetal malformations.[8] When acyclovir was administered by gavage to mice in doses up to 450 mg/kg/d (30 times human therapeutic doses), no adverse effects or toxicity appeared in reproduction or development over two generations.[8] The effect of acyclovir on mammalian embryonic development in cell culture showed that even extremely large doses did not result in individual gene damage.[9] Chromosomal damage in cultured human lymphocytes has been reported at acyclovir concentrations 25 times higher than peak levels (1100 μmol/L or 250 μg/mL administered intravenously).[6]

Because of the lack of prospective data on pregnancy and acyclovir, the Burroughs Wellcome Company and the Centers for Disease Control and Prevention have established the Acyclovir in Pregnancy Registry to evaluate reported cases of gestational exposure to the drug. The address for this service is: Acyclovir in Pregnancy Registry, Division of Epidemiology, Burroughs Wellcome Co., 3030 Cornwallis Road, Research Triangle Park, NC 27709; phone: 1-800-722-9292, ext. 8465.

Acute Toxicity

Oral acyclovir is generally well tolerated, but serious adverse effects, including crystallization within the renal tubules, have been reported when the drug is administered intravenously. This nephrotoxicity, which is thought to be caused by the precipitation of acyclovir in the nephron, occurs in less than 5% of hospitalized

patients when the drug is administered intravenously.[10] Such crystallization can result in obstructive nephropathy that can lead to renal failure and anuria and may be manifested by increases in serum blood urea nitrogen (BUN) and creatinine levels. Renal insufficiency usually is completely reversible with discontinuation of acyclovir. However, if acute renal failure and anuria occur, dialysis should be considered to enhance elimination of the drug. Because of the potential for renal toxicity, the drug should be administered over 1 hour, patients should be well hydrated during intravenous therapy, a urine volume of at least 500 mL per 24 hours should be maintained, and the BUN and creatinine levels monitored closely.[11] There has been one case report of nephrotoxicity with high-dose oral acyclovir (800 mg 5 times a day) in a patient also on propoxyphene,[12] but there have been no reports of increased renal toxicity in pregnant patients receiving either form of the drug.

Intravenous acyclovir can cause phlebitis at the injection site as a result of the drug's high pH. Acyclovir's other side effects include headache, lethargy, tremor, vomiting, seizures, and delirium. Chronic suppressive therapy of genital herpes, with either oral or intravenous acyclovir, can cause nausea in 5% and diarrhea in approximately 2% of patients.[2,3] Skin rash has been reported in 1% to 2% of patients.[3] Patients with underlying neurologic disease or renal impairment should be monitored carefully for signs of central nervous system toxicity.[13] Generally, acyclovir is well tolerated by most patients.

Inadvertent First-Trimester Exposure

An estimated 30% to 50% of acyclovir users in the United States are women of child-bearing age who take the drug for suppression of recurrent genital herpes or complicated VZV.[1] The likelihood of inadvertent first-trimester exposure to acyclovir illustrates the need for physicians to provide patients with current data on the potential for fetal harm. The Acyclovir in Pregnancy Registry, recently summarized by Andrews et al,[1] includes early acyclovir exposures that were prospectively reported to Burroughs Wellcome. Of 239 first-trimester exposures, there were 24 spontaneous abortions, 47 elective abortions, 159 live births of normal infants, and 9 live births with congenital malformations. None of these anomalies followed a consistent pattern, and the authors note that the anomaly rate is similar to that of the general population. The most recent update of this registry, which includes 171 additional first-trimester exposures, confirms this trend (Burroughs Wellcome Company, written communication, June 1993).

Aside from the registry, there are few reports of first-trimester exposures to acyclovir. Five published cases[14–17] resulted in the birth of four normal infants (three at term, one at 42 weeks) and one elective termination of pregnancy. Initial exposures ranged from 1 to 13 weeks' gestation. A report from Great Britain identified 24 additional pregnant patients exposed to acyclovir during the first trimester (Inman WHW. Prescription event monitoring studies. Prescription Monitoring Event News, Sept 1988), 18 of whom gave birth to normal infants, 1 who had a spontaneous abortion, and 5 who had elective abortions.

While the total number of reported cases of first-trimester exposures to acyclovir is too small to justify conclusions regarding the drug's safety, available data do not point to a pattern of increased maternal or fetal adverse outcomes. However, as a nucleoside analogue, acyclovir is potentially teratogenic, and its use should be restricted to situations in which benefits clearly outweigh potential fetal risks. Although acyclovir lacks FDA approval for use during pregnancy, there seems to be a consensus in the literature warranting its use in some situations.

Disseminated Maternal Herpes Simplex Virus Infection

The initial episode of genital HSV infection in a pregnant woman seronegative for HSV types 1 or 2 (known as primary genital HSV) is often marked by severe, prolonged pain and fever and the appearance of distal lesions.[6] Rarely, during the second half of pregnancy, primary genital HSV infection can disseminate as a result of the normal decline in maternal cell-mediated immunity that occurs during pregnancy.[18] This dissemination can lead to encephalitis, pneumonitis, disseminated intravascular coagulation, and, most commonly, hepatitis with very high rates of maternal and fetal mortality.[19] Because of its life-threatening nature, patients with primary genital HSV infections who begin to manifest signs of dissemination (coagulopathy, encephalopathy, pneumonitis, or hepatitis) should be started on intravenous acyclovir,[19,20] with a suggested dose of 7.5 mg/kg every 8 hours.[6] Reported lengths of therapy range from 5 days[21] to 11 days,[22] based on the rate of maternal response. Watts suggests continuing 7.5 mg/kg intravenously every 8 hours until the mother's condition improves, then switching to oral acyclovir 200 mg every 4 hours to complete a 14-day course.[3]

It must be noted that there are no data to support the use of acyclovir in milder cases of primary genital HSV, or in cases developing early in pregnancy that have a smaller chance of dissemination. In these cases, the potential risk of teratogenicity must be weighed against the small risk of maternal dissemination of HSV. No

evidence exists comparing oral and intravenous acyclovir in severe primary genital HSV, although authorities recommend the intravenous route, at least until the mother's condition improves.[3,19,20]

Late Primary Genital HSV Infection

Even without dissemination, primary genital HSV increases the risk of an adverse outcome for the fetus or newborn.[20,23] While first-trimester infections may result in severe congenital malformations or spontaneous abortion,[20] fetal risks, including a high incidence of fetal intrauterine growth retardation, premature birth, and neonatal HSV,[23] are greatest during the second and third trimesters. Because of these risks, authorities argue that acyclovir therapy should be strongly considered to treat late primary genital HSV infections.[6,20] Brown and Baker[6] suggest a dose of 7.5 mg/kg intravenously every 8 hours (published therapeutic durations range from 5 days[24] to 12 days[15]). Because there is no recommended length of intravenous therapy for late primary HSV, it seems reasonable to take a therapeutic approach analogous to that of disseminated HSV with a switch to oral acyclovir (based on the rate of maternal response) to complete a 14-day antiviral course.

Severe Varicella-Zoster Infections and Varicella Pneumonia

Varicella-zoster infections in pregnancy, as in nonpregnant states, range from mild to severe. Management of milder cases of varicella during pregnancy, which has been reviewed elsewhere,[25,26] does not require acyclovir therapy. Similarly, it is not known if acyclovir therapy prevents congenital varicella, a syndrome that results from maternal infections at 12 to 16 weeks' gestation and is associated with dermatomal skin defects, microcephaly, intrauterine growth retardation, microphthalmia and other eye abnormalities, and limb atrophy.[25] The decision to treat patients with mild first-trimester VZV infections should be made on an individual basis, taking into account the severity of the mother's infection and the potential for teratogenic effects of acyclovir.[26]

The literature suggests that maternal treatment with acyclovir be reserved for severe, systemic varicella infections. Varicella pneumonia, which is by far the worst complication of maternal varicella infection,[26] accounts for a large portion of the increased mortality from this virus during pregnancy.[6] Its incidence correlates with the extent of the pregnant woman's cutaneous disease, fever, and systemic symptoms.[26] There have been 25 reported cases of intravenous acyclovir used during pregnancy to treat varicella pneumonia.[14,27–40] Dosages ranged from 5 mg/kg to 15 mg/kg every 8 hours for 6 to 12 days, and treatment was initiated at 12 to 36 weeks' gestation. Of these cases, there were 21 normal infant deliveries (one at 36 weeks with chicken pox), 3 neonatal deaths (at 26, 30, and 34 weeks) and 3 maternal deaths. One pregnancy was electively terminated at 15 weeks. Brown and Baker[6] state that "because of its substantial morbidity, and even though prospective data proving efficacy and fetal safety are lacking, maternal varicella pneumonia should be treated with [intravenous] acyclovir."[6,p529] Other authorities[26] concur, adding that acyclovir therapy also should be given to pregnant women with severe varicella because the onset of varicella pneumonia correlates with extensive systemic and cutaneous disease. There are no established guidelines for dosage and length of therapy for severe maternal varicella infections, but 10 to 15 mg/kg every 8 hours intravenously for 7 days appears adequate and seems not to cause adverse maternal or fetal side effects.[28]

Problematic Uses

Other uses of acyclovir in pregnancy remain problematic. Ciraru-Vigneron and colleagues[41] reported treating 9 women with acyclovir after 36 weeks' gestation to suppress symptomatic recurrences of genital herpes in an attempt to avoid cesarean section because of its associated maternal morbidity. While this approach seems reasonable, it is not known if acyclovir suppresses genital viral shedding during pregnancy or simply causes symptomatic lesions to become asymptomatic and undetectable.[6]

It is also unclear whether acyclovir should be used in mild or early cases of primary genital HSV infections.[6] Since patients with first-episode genital HSV infections (ie, those who previously have had HSV-1 or HSV-2 infections at another bodily site) are at no greater risk for dissemination than are women with recurrent genital herpes, they need not be treated with acyclovir.[20]

Although the use of acyclovir in ophthalmic zoster has not been specifically addressed, considering the guidelines reported for severe maternal varicella-zoster disease, "it would seem reasonable to make decisions about therapy [for ophthalmic zoster] on a case-by-case basis, evaluating such factors as the severity of the disease and the initial ophthalmologic findings."[42]

Conclusions

In this paper, we reported a case of first-trimester exposure to the antiviral drug acyclovir, highlighting the

emotional impact of the exposure on the mother. We also have reviewed reports of its use during pregnancy and in situations where its gestational use appears justified. Limited data from clinical, laboratory, and animal studies show no consistent pattern of excessive maternal or fetal morbidity when acyclovir is used during pregnancy. However, since there have been relatively few reports of its use during all stages of pregnancy, it is difficult to draw firm conclusions regarding the effects on mother or fetus. The Acyclovir in Pregnancy Registry enables physicians to offer their patients more informed counsel about gestational exposure to the drug, which helps patients make rational decisions regarding their pregnancies.

Despite the potential risks, there are several circumstances in which the benefits of acyclovir therapy in pregnancy appear to outweigh possible fetal harm. These include severe, late-onset (eg, second or third trimester), or disseminated primary HSV infections and severe varicella-zoster infections, especially varicella pneumonia.

For severe HSV infections, one suggested regimen is intravenous acyclovir 7.5 mg/kg every 8 hours for a number of days, followed by oral acyclovir 200 mg every 4 hours to complete a 14-day course of antiviral therapy based on the rate of maternal improvement.[3] For severe varicella infections, 10 to 15 mg/kg intravenously every 8 hours for 7 days appears adequate.[28] Whenever acyclovir is used intravenously, the patient should be well hydrated with urine output maintained above 500 mL/h and serum BUN and creatinine levels closely monitored to avoid renal toxicity.[10,11]

Acyclovir is not recommended for the treatment of milder HSV or varicella infections, first-episode genital herpes in women who have had HSV at other bodily sites, or recurrent HSV lesions occurring at the end of pregnancy.

References

1. Andrews EB, Yankasakas BC, Cordero JF, Schoeffler K, Hampp S. Acyclovir in pregnancy registry: six years' experience. Obstet Gynecol 1992; 79:7–13.
2. Laskin OL. Acyclovir pharmacology and clinical experience. Arch Intern Med 1984; 144:1241–6.
3. Watts HD. Antiviral agents. Obstet Gynecol Clin North Am 1992; 19:563–85.
4. Frenkel LM, Brown ZA, Bryson YJ, Corey L, Unadkat JD, Hensleigh PA, et al. Pharmacokinetics of acyclovir in the term human pregnancy and neonate. Am J Obstet Gynecol 1991; 164:569–76.
5. Kingsley S. Fetal and neonatal exposure to acyclovir [abstract]. Presented at the Second World Congress on Sexually Transmitted Diseases, Paris, June 1986.
6. Brown AZ, Baker DA. Acyclovir therapy during pregnancy. Obstet Gynecol 1989; 73:526–31.
7. Van Dyke RB, Connor JD, Wyborny C, Hintz M, Keeney RE. Pharmacokinetics of orally administered acyclovir in patients with herpes progenitalis. Am J Med 1982; 73:172–5.
8. Moore HL, Szczech GM, Rodwell DE, Kapp RW, deMiranda P, et al. Preclinical toxicology studies with acyclovir: teratologic, reproductive and neonatal tests. Fundam Appl Toxicol 1983; 3:560–8.
9. Klug S, Lewandowski C, Blankenbur G, Merker HJ, Neubert D. Effect of acyclovir on mammalian embryonic development in culture. Arch Toxicol 1985; 58:89–96.
10. Straus SE, Ostrove JM, Inchauspe G, Felser JM, Frefield A, et al. Varicella-zoster virus infection. Ann Intern Med 1988; 108: 221–7.
11. Acyclovir. In: McEvoy GK, ed. American Hospital Formulary Service. Bethesda, Md: American Society of Hospital Pharmacists, 1993:365–73.
12. Eck P, Silver SM, Clark EC. Acute renal failure and coma after high dose acyclovir [letter]. N Engl J Med 1991; 325:1539–44.
13. Feldman S, Rodman J, Gregory B. Excessive serum concentrations of acyclovir and neurotoxicity. J Infect Dis 1988; 157:385–8.
14. Clark GPM, Dobson PM, Thickett A, Turner NM. Chickenpox pneumonia, its complications and management. Anaesthesia 1991; 46:376–80.
15. Foidart JM, Lambotte R. Treatment of severe genital herpes simplex virus (HSV) infection during pregnancy with intravenous acyclovir [abstract 43–10]. Presented at the Second World Congress of Sexually Transmitted Diseases, Paris, June 25–28, 1986.
16. Horowitz GM, Hankins GD. Early second trimester use of acyclovir in treating herpes zoster in a bone marrow transplant patient, case report. J Reprod Med 1992; 37:280–2.
17. Kundsin RB, Falk L, Hertig AT, Horne HW. Acyclovir treatment of twelve unexplained infertile couples. Int J Fertil 1987; 32: 200–4.
18. Weinberg ED. Pregnancy-associated depression of cell-mediated immunity. Rev Infect Dis 1984; 6:814–31.
19. Brown ZA, Watts H. Antiviral therapy in pregnancy. Clin Obstet Gynecol 1990; 33:276–89.
20. Baker DA. Herpes and pregnancy: new management. Clin Obstet Gynecol 1990; 33:253–7.
21. Cox SM, Phillips LE, DePaolo HD, et al. Treatment of disseminated herpes simplex virus in pregnancy with parenteral acyclovir. A case report. J Reprod Med 1986; 31:1005–7.
22. Frieden FJ, Ordorica SA, Goodgold AL, Hoskins IA, Silverman F, Young BK. Successful pregnancy with isolated herpes simplex virus encephalitis. Case report and review of the literature. Obstet Gynecol 1990; 75:511–3.
23. Brown ZA, Vontver LA, Benedetti J, et al. Effects on infants of a first episode of genital herpes during pregnancy. N Engl J Med 1987; 317:1246–51.
24. Key TC, Resnik R, Dittrich HC, Reisner LS. Successful pregnancy after cardiac transplantation. Am J Obstet Gynecol 1989; 160: 367–71.
25. Fox GN, Strangarity JW. Varicella-zoster virus infections in pregnancy. Am Fam Physician 1989; 39:89–98.
26. Prober CG, Gershon AA, Grose C, McCracken GH, Nelson JD. Consensus: varicella-zoster infections in pregnancy and the perinatal period. Pediatr Infect Dis J 1990; 9:865–9.
27. Boyd K, Walker E. Use of acyclovir to treat chickenpox in pregnancy. BMJ 1988; 296:393–4.
28. Broussard RC, Payne DK, George RB. Treatment with acyclovir of varicella pneumonia in pregnancy. Chest 1991; 99:1045–7.
29. Cox SM, Cunningham FG, Luby J. Management of varicella pneumonia complicating pregnancy. Am J Perinatol 1990; 7:300–1.
30. Eder SE, Apuzzio JJ, Weiss G. Varicella pneumonia during pregnancy. Am J Perinatol 1988; 5:16–8.
31. Esmonde TF, Herdman G, Anderson G. Chickenpox pneumonia: an association with pregnancy. Thorax 1989; 44:812–5.
32. Glaser JB, Loftus J, Ferragamo V, Mootabar H, Castellano M. Letter. N Engl J Med 1986; 315:1416.
33. Hankins GDV, Gilstrap LC, Patterson AR. Acyclovir treatment of

varicella pneumonia in pregnancy [letter]. Crit Care Med 1987; 15:336–7.
34. Hockberger RS, Rothstein RJ. Varicella pneumonia in adults: a spectrum of disease. Ann Emerg Med 1986; 15(8):931–4.
35. Hollingsworth HM, Pratter MR, Irwin RS. Acute respiratory failure in pregnancy. J Intensive Care Med 1989; 4:11–34.
36. Landsberger EJ, Hager DW, Grossman JH. Successful management of varicella pneumonia complicating pregnancy: a report of three cases. J Reprod Med 1986; 31:311–4.
37. Leen CL, Mandal BK, Ellis ME, Brettle RP. Acyclovir and Pregnancy [letter]. BMJ 1987; 294:308.
38. Lotshaw RR, Keegan JM, Gordon HW. Parenteral and oral acyclovir for management of varicella pneumonia in pregnancy: a case report with review of literature. W V Med J 1991; 87:204–6.
39. Smego RA, Asperilla MD. Use of acyclovir for varicella pneumonia during pregnancy. Am Coll Obstet Gynecol 1991; 78:1112–6.
40. White RG. Chickenpox in pregnancy [letter]. BMJ 1988; 296: 864.
41. Ciraru-Vigneron N, Nguyen TLR, Blondeau MA, Brunner C, Barrier J. Value of the prescription of acyclovir at the end of pregnancy in genital herpes. A new protocol for preventing the risk of neonatal herpes. Presse Med 1987; 16:128.
42. Fox GN. Reply to letter. Oral acyclovir in maternal zoster. Am Fam Physician 1989; 40:55.

See editorial on page 121