

Pregnancy Outcomes following Systemic Prenatal Acyclovir Exposure: Conclusions from the International Acyclovir Pregnancy Registry, 1984–1999

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BACKGROUND: Oral acyclovir is commonly used for genital herpes and other herpesvirus infections. Data on potential fetal risk are extremely limited. From 1984 to 1998, the Acyclovir in Pregnancy Registry monitored birth outcomes of women exposed to oral or intravenous acyclovir during pregnancy. This report describes the final results. **METHODS:** The registry was publicized to health care providers most likely to diagnose pregnancy; providers called the registry telephone number, then mailed in a brief questionnaire. Pregnancy outcomes were categorized either as outcomes with birth defects or outcomes without birth defects, subcategorized as live births, spontaneous pregnancy losses (including stillbirths), and induced abortions. Birth defects were defined using a modification of the CDC definition for birth defects surveillance systems. Observed rates were compared to the rate (3.2%) of birth defects expected in the general population. **RESULTS:** Between June 1, 1984 and June 30, 1998, 1695 pregnancies exposed to oral or IV acyclovir were registered; 461 (27%) were lost to follow-up. A total of 1234 pregnancies in 24 countries were followed, with a total of 1246 outcomes. Among 1246 pregnancy outcomes, 756 involved acyclovir exposure in the first trimester, 197 in the second trimester, and 291 in the third trimester. Among live births with first trimester acyclovir exposure, risk of birth defects was 19 of 596 (3.2%; 95% CI, 2.0–5.0%). No unusual defects or pattern of defects were apparent. **CONCLUSIONS:** The observed rates and types of birth defects for pregnancies exposed to acyclovir did not differ significantly from those in the general population. *Birth Defects Research (Part A) 70:201–207, 2004.* Published 2004 Wiley-Liss, Inc.[†]

Key words: genital herpes; HSV; pregnancy; acyclovir treatment

INTRODUCTION

Acyclovir (ZoviraxTM) is currently available as a prescription drug in oral, IV, and topical formulations for use in the treatment of herpesvirus infections. Marketing research and epidemiologic studies in the United States suggest that the greatest use of acyclovir is for oral treatment of genital herpes. It is also used for treatment of severe and complicated cases of primary varicella (chickenpox) and varicella zoster (shingles). Among acyclovir users in the U.S. population, an estimated 30–50% are women of childbearing age (Johnson et al., 1990). Oral acyclovir was approved by the U.S. FDA (Food and Drug Administration) in 1984 and classified at that time

as a Category C drug, i.e., one that should not be used in pregnancy unless the potential therapeutic benefits outweigh the potential risks to the fetus.

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Acyclovir crosses the placenta, is concentrated and excreted by the fetal kidney, and is found in amniotic fluid and fetal tissue. In late gestation, maternal acyclovir pharmacokinetics are similar to those of nonpregnant adults. In humans, acyclovir is concentrated in the amniotic fluid; however, there is no accumulation in the fetus (Frenkel et al., 1991). Human trials of new drugs usually exclude pregnant women; therefore, information on safety of use during pregnancy is usually not available prior to FDA approval. For acyclovir, extensive reproductive toxicology studies in animal models were conducted under international standards prior to drug approval and did not show a teratogenic effect (Moore et al., 1983). Subsequent studies using a newer model showed head and tail abnormalities in rats at higher doses; higher doses were associated with reversible maternal nephrotoxicity, but lower doses were not (Stahlmann et al., 1988).

Because widespread acyclovir use by sexually active women of childbearing age was likely to lead to inadvertent exposures during early pregnancy, and since data on human teratogenic risks of acyclovir were extremely limited, a registry of use during pregnancy was established in June 1984 to monitor early signals of potential risks to the fetus. Interim results have been reported previously (Andrews et al, 1992; CDC, 1993a). This report describes the final results of the Acyclovir Pregnancy Registry, which was closed to new enrollment in June 1998.

MATERIALS AND METHODS

After licensure of oral acyclovir, the Acyclovir in Pregnancy Registry to monitor birth defects was established in June 1984 as a voluntary commitment of the manufacturer to the FDA. The registry was managed by the manufacturer, GlaxoSmithKline (GSK, formerly Glaxo Wellcome and Burroughs Wellcome), under the active guidance of an advisory committee composed of individuals from GSK, the Centers for Disease Control and Prevention (CDC), and academic researchers at institutions with expertise in sexually transmitted diseases, perinatology, teratology, pharmacology, epidemiology, and clinical obstetrics and gynecology, including most of the coauthors of this report (K.M.S., A.D.W., J.F.C., Z.B., E.R.A., and E.B.A.). The committee reviewed all data semiannually before issuing interim reports that were sent to health professionals who had or were likely to have patients with inadvertent early-pregnancy exposure to acyclovir.

Pregnancies exposed to acyclovir were reported to the registry by telephone by health care providers or, in a few cases, by pregnant women. Registry staff obtained information on acyclovir exposure and pregnancy outcomes through mailed questionnaires, using frequent reminders to minimize loss to follow-up. A case for whom a registration form was at least partially completed was considered registered. Follow-up usually extended only through delivery or the mother's first postpartum visit, although abnormalities identified and reported subsequently are included in the registry data. The registry was publicized regularly through targeted announcements in obstetrics and teratology newsletters and journals, the CDC STD treatment guidelines (CDC, 1993b, 1998b), the Report of the Committee on Infectious Diseases ("Red Book") (AAP, 1997), and exhibits and presentations at scientific meetings.

Exposed pregnancies are those in which the mother is treated with oral and/or IV acyclovir at any time in preg-

nancy. Topical acyclovir was excluded from formal review because of its low systemic absorption. Exposures were classified by the earliest trimester of use. Prospective reports (those reported before knowledge of pregnancy outcome or results of prenatal testing) were analyzed separately from retrospectively reported cases. Prospective reports are less subject to reporting biases and can be used to calculate rates of pregnancy outcomes. Retrospective reports are subject to selective reporting based on outcome status and are not useful in calculating rates, but are valuable for identifying any unusual patterns of abnormal outcomes. Enrollment of new pregnancies ended on June 30, 1998 and follow-up ended on April 30, 1999.

Pregnancy outcomes were classified into two categories: outcomes with birth defects and outcomes without birth defects; the latter category was further subclassified into three subcategories: live births, spontaneous pregnancy losses (including stillbirths), and induced abortions. Infants with birth defects were defined using a broader modification of the definition for birth defects surveillance programs (CDC, 1998a): any live or stillborn infant with a structural or chromosomal abnormality diagnosed before the infant is one year of age, including defects in infants detected prior to 20 weeks gestation or weighing less than 500 gm. In addition to the list of birth defects recognized by the CDC (CDC, 1998a), the registry includes additional minor defects, such as those in infants <2500 gm that are attributable to prematurity itself (e.g., patent ductus arteriosus, inguinal hernia), as well as Mongolian spots and bilateral hydroceles. All defects were classified by a physician from the CDC Division of Birth Defects and Developmental Disabilities, who was a member of the advisory committee. On a case by case basis, the registry also closely reviewed each infant with three or more conditions, to determine if the combination would constitute a defect, even if each event alone would not have constituted a defect according to CDC guidelines. Infants with only transient, infectious, or biochemical abnormalities were classified as being without birth defects unless there was a possibility that the condition reflected an unrecognized birth defect.

For each infant with a birth defect, careful consideration was given to timing of exposure relevant to the origins of the defect, other known or likely causes (e.g., a recognized genetic or chromosomal defect or exposure to a known teratogen), whether observed defects were novel, and whether there was a unique combination of defects. The entire registry database was regularly scrutinized to assess any deviation from the rate of defects expected in the general population; uniqueness or patterns of defects that might suggest a common cause, and whether the diversity of defects was sufficient to suggest no apparent single cause.

Pregnancy outcomes were stratified by the earliest trimester of exposure. Gestational weeks were counted from the date of the last menstrual period, with the second trimester beginning at week 14 and the third trimester beginning at week 28. Calculations of risk for birth defects were made by dividing the number of infants with birth defects by the total number of infants with and without birth defects. The 95% confidence intervals (CIs) were calculated using the Fleiss method (Fleiss, 1981). Observed rates were compared to the rate (3.15%) expected in the general population, estimated using U.S. birth defects sur-

Table 1
Prospective Registry—Acyclovir Exposure in Pregnancy by Earliest Trimester of Exposure and Outcome*

Earliest trimester of exposure	Outcomes with birth defects	Outcomes without birth defects ^a			Total
		Live births without birth defects	Spontaneous pregnancy losses	Induced abortions	
Unspecified	0	1	0	1	2
First	19	577 ^b	77	83	756 (61%)
Second	2	194 ^c	0	1	197 (16%)
Third	7	282 ^d	2	0	291 (23%)
Total	28	1054	79	85	1246 (100%)

*This table excludes patients with exposure to topical acyclovir only. For definition of inclusions see section entitled Materials and Methods.

^aBirth defect not reported but cannot be ruled out.

^bIncludes seven sets of twins.

^cIncludes two sets of twins.

^dIncludes three sets of twins.

veillance data (Honein et al., 1999b). Statistical power was calculated for the attained sample size using exact binomial probabilities. Because of the discrete nature of this distribution, an alpha level of 0.05 did not exist for the sample sizes assessed, and the next lowest probabilities were chosen to define alpha.

Spontaneous pregnancy losses and induced abortions were excluded from the denominator. Since risk of spontaneous abortion in early pregnancy is high (14–22%) (Kline et al., 1989), and since pregnancies were reported to this registry at variable and sometimes imprecise times during gestation, these registry data cannot be used to calculate risk of spontaneous pregnancy loss due to drug exposure. Any defects observed and reported from early pregnancy losses, however, would have been counted among the birth defects even though the total number of losses would not have been included in the denominator.

RESULTS

Between June 1, 1984 and June 30, 1998, 1695 cases of prenatal exposure to oral or IV acyclovir during pregnancy were registered prospectively. A total of 461 (27%) cases were lost to follow-up and are not included in this report. A total of 1234 pregnancies were successfully followed to determine pregnancy outcomes (prospective cases). A total of 1246 outcomes were obtained, including 12 sets of twins. Baseline information on cases lost to follow-up is too limited to allow comparison with complete case reports.

Prospectively registered cases originated from 24 countries. A total of 65% were from the United States, 14% from France, 9% from the United Kingdom, and 5% from Germany. The remaining 7% came from Australia, Austria, Bermuda, Brazil, Canada, Czech Republic, Denmark, Finland, Greece, Ireland, Italy, Japan, Malaysia, the Netherlands, New Zealand, Oman, South Africa, Spain, Sweden, and Switzerland.

Among the 1246 outcomes, 61% involved exposures in the first trimester, 16% in the second trimester, and 23% in the third trimester (Table 1). A total of 28 cases with birth defects were identified; 19 from women with first trimester exposure, two with second trimester exposure, and seven with third trimester exposure. Of the 749 pregnancies reported with earliest exposure in the first trimester, there were 756 pregnancy outcomes, including seven sets of twins. Of these 756 outcomes, there were 19

infants with birth defects, 77 spontaneous pregnancy losses (including one stillbirth), 83 induced abortions, and 577 infants without birth defects. A total of 195 second-trimester exposures were reported, with 197 outcomes (including two sets of twins). Of the 197 outcomes, there were two infants with birth defects, one induced abortion, and 194 infants without birth defects. Of the 288 pregnancies reported with earliest exposure in the third trimester, there were 291 pregnancy outcomes (including three sets of twins). There were seven cases with birth defects, two stillbirths, and 282 infants without birth defects. Two reports were received in which the trimester of exposure was unknown; the outcomes include one induced abortion and one infant without a birth defect. No unusual defect or pattern of defects was apparent (Tables 2–4). Risk of birth defects among live births exposed to acyclovir in the first trimester was 19 of 596 (3.2%; 95% CI, 2.0–5.0%) and for exposures during any trimester was 28 of 1082 (2.6%; 95% CI, 1.8–3.8%).

Information was available on the maternal indications for acyclovir use during pregnancy for 1206 (97%) of outcomes. Of these, 54% of indications were genital herpes, 16% for nongenital herpes simplex virus (HSV) infections only, 27% for varicella-zoster virus (VZV) infections only, 2% for unspecified HSV infections, and 1% for other conditions. No pattern or relationship between outcomes and maternal treatment indications was evident.

Retrospective reports (cases with a known outcome at the time of reporting) were also collected and reviewed. Retrospective reports can be biased toward the reporting of more unusual and severe cases and are less likely to be representative of the general population. Therefore, calculation of rates from these reports is inappropriate. The purpose of summarizing these retrospective reports was to assist in the detection of any unusual patterns among the reported cases. Among retrospective acyclovir exposure reports from 22 countries, 47 infants had birth defects that were generally similar to those reported prospectively; no apparent pattern existed among these defects.

DISCUSSION

This registry focused on birth defects detected and reported during the perinatal period. Methodologic limita-

Table 2
Prospective Registry—Birth Defects from Pregnancies with First-Trimester Acyclovir Exposure

Case	Route	Dose	Indication	Infant sex	Gestational weeks	Outcome
A	Oral	800 mg/day from week 3–3	HSV oral	F	40	Hemangiomas, 2 × 5 cm on forehead, 2 × 2 cm on posterior neck, 3 × 2 cm on occiput.
B	Oral	200 mg/day from week 5–5	HSV oral	?	39	Diaphragmatic hernia; severe respiratory distress syndrome.
	Oral	Unknown dose from week 0–1	HSV genital			
C	Oral	Unknown dose/exposure time during first trimester	HSV genital	F	20	Neural tube defect of thoracic spine, spina bifida with meningocele, and diastematomyelia. Induced abortion following detection.
	Oral	1000 mg/day from week 5–5	HSV oral			
D	Oral	800 mg/day from week 1–3	HSV genital	M	40	Healthy at birth. At five months, scoliosis was noted; at nine months, convulsions, spastic paralysis, delayed physical, and mental development, attributed to an inherited genetic defect suspected to have been caused by a fragile X chromosome.
	Topical	week 0–3	HSV genital			
E	Oral	200 mg/day from week ?–?	HSV genital	M	41	Pyloric stenosis.
F	Oral	800 mg/day from week 3–3	HSV genital	M	40	Pyloric stenosis, mild IUGR, breech birth.
G	Oral	1000 mg/day from week 1–1	HSV genital	M	?	Hip dysplasia causing hypermobility.
H	Oral	400 mg/day from week 8–8	Herpes zoster	F	34	Ascites, cardiomegaly, cardiomyopathy, hydrocephalus, calcified foci in the CNS, premature birth. At one month, respiratory insufficiency, heart failure, and hydrocephalus.
I	Oral	1000 mg/day from week 3–4	HSV genital	M	39	Cleft palate and micrognathia; respiratory distress syndrome.
J	Oral	1000 mg/day from week 5–6	HSV oral	M	39	Lower limb deformities. Reporter: "Probably due to amniotic band syndrome."
K	Oral	600 mg/day from week 0–5	HSV genital	M	38	Unilateral intermittent ureteral pelvic junction (UPJ) obstruction accompanied by a left posterior/lateral wall bladder-based diverticulum ("most likely representing a hutch diverticulum. Both conditions may require surgery").
L	Oral	800 mg/day from week 4–4	HSV oral	M	38	Pyloric stenosis.
M	Oral	800 mg/day from week 4–5	HSV genital	F	39	Congenital blindness, cessation in the development of iris and retina, and retinal malformation.
N	Oral	3200 mg/day from week 13–14	VZV chickenpox	M	40	Spontaneous resolution of nondescended testes at two months of age.
O	Oral	1000 mg/day from week 4–5	HSV genital	F	36	Initial report: Infant with IUGR, but no birth defects. Upon follow-up (nine months later) reported to have plagiocephaly.
P	Oral	800 mg/day from week 4–4	HSV genital	F	41	Cleft lip.
Q	Oral	800 mg/day for unknown time in first trimester	Herpes zoster	F	39	Malformation of the distal joints of the 2nd to 5th fingers on the left hand, diagnosed as hypoplasia congenita ossis. X-rays of the hands showed slight asymmetry, the left hand being slightly smaller than the right. The phalanges on the left hand were smaller than those on the right, with a suggestion of webbing between the 3rd and 4th, and 4th and 5th fingers. Physical examination at nine days of age indicated good function of both fingers with a natural grasping reflex. In addition, sonography during pregnancy indicated hydronephrosis of the right kidney. No follow-up received on repeat sonography following birth.
R	Oral	200 mg/day from week 3–4	HSV genital	M	12	Induced abortion at 12 weeks. Down syndrome, trisomy 21 detected by chorionic villus biopsy.
S	Oral	800 mg/day from week 1–7	HSV genital	F	38	Congenital absence of right fibula and three toes.

Table 3
Prospective Registry—Birth Defects from Pregnancies with Second-Trimester Acyclovir Exposure

Case	Route	Dose	Indication	Infant sex	Gestational weeks	Outcome
a	Oral	4800 mg/day from week 22–23	Herpes zoster	F	40	Mild pulmonary valve stenosis.
b	Oral Topical	1000 mg/day from week 26–27 Week 26–27	HSV genital HSV genital	F	40	Positional talipes, no surgery anticipated.

tions of this voluntary registry have been reviewed previously (Andrews and Tilson, 1988; Andrews et al., 1992). Underascertainment of birth defects was possible, since follow-up was obtained from the mothers' health care providers in the postnatal period, rather than from the infants' providers, who would have been more likely to observe defects not readily apparent during the neonatal period (e.g., cardiac and intestinal abnormalities). Reporting of exposed pregnancies was entirely voluntary, and may have been biased toward high-risk or low-risk pregnancies. Exclusion of spontaneous abortions or induced abortions without identified birth defects from the denominator may bias the calculation of risk of birth defects, since birth defects among these outcomes are not always recognized. The level of underascertainment of acyclovir exposures during pregnancy cannot be estimated but is likely to be great, given the age and gender utilization patterns of acyclovir and average fertility rates (Andrews et al., 1992).

The value of pregnancy registries is receiving public attention, and was the focus of a March 2000 FDA Advisory Committee meeting. This pregnancy follow-up study was designed specifically to detect and quantify birth defects that could be readily identified after delivery to address the first-line question: is there a signal for a major increase in the risk of teratogenicity with acyclovir? For that question, the methods employed were appropriate. In order to obtain a large number of exposures and secure the cooperation of reporting physicians who were not seasoned research investigators, we adopted a streamlined approach to data collection, in which many potentially interesting data points were sacrificed to maximize completeness of information on a few key variables. Likewise, we chose to limit follow-up to the period immediately following delivery to maximize the number of outcomes in the study. Extended follow-up would have required com-

plex procedures and multiple providers, with a much smaller and potentially biased sample. Had a signal emerged from this study, we might have chosen a different type of study design for confirmation.

Neither the observed rate of birth defects (3.2%) for pregnancies exposed to acyclovir in the first trimester, nor the rate (2.6%) for exposure at any time during pregnancy, differ from the expected rate (3.2%) in the general population (Honein et al., 1999b). This finding, together with the absence of any uniqueness or consistent patterns of defects identified in the prospective or retrospective reports, should provide some reassurance in counseling women following inadvertent prenatal acyclovir exposure. These registry data are sufficient to exclude a seven-fold increase in risk of overall birth defects, but cannot address the risk for rare or specific defects or for those detected after the postnatal period. The risk of specific birth defects in the general population may be as low as 1–2 per 1000 live births (or less), and the sample size of this registry is not adequate to detect low levels of increased risk. For a specific birth defect with a baseline occurrence of 1 in 1000 live births, the registry sample size of 596 first-trimester exposures allows an 80% chance (80% power) of correctly detecting a 7.2-fold increase in risk of occurrence of birth defects, assuming an alpha level of 0.02 (a 2% chance of erroneously concluding that the rate is increased above the baseline level). The registry sample size of 1082 exposed births allows an 80% chance (80% power) of correctly detecting a 5.1-fold increase in occurrence of birth defects, assuming an alpha level of 0.03 (a 3% chance of erroneously concluding that the rate is higher than baseline).

Three male infants (3/596, 0.5%) had pyloric stenosis. The expected rate in the general population is 0.1–0.3% (Honein et al., 1999b); however, rates vary widely by sex and race/ethnicity. Rates are typically four times higher

Table 4
Prospective Registry—Birth Defects from Pregnancies with Third-Trimester Acyclovir Exposure

Case	Route	Dose	Indication	Infant sex	Gestational weeks	Outcome
i	Oral	200 mg from week 36–37	HSV genital	M	37	Transposition of the great vessels and ventricular septal defect.
ii	Oral Topical	1000 mg/day from week 39–41 week 39–41	Herpes zoster Herpes zoster	F	41	Hip dysplasia.
iii	Oral	1000 mg/day from week 35–40	HSV genital	M	40	Positional talipes.
iv	Oral Oral	800 mg/day from week 28–28 800 mg/day from week 36–40	HSV genital HSV genital	M	40	Down syndrome diagnosed by chromosomal analysis, skin blister culture negative for herpes.
v	Oral	4000 mg/day from week 37–38	Herpes zoster	M	38	Craniosynostosis; surgically repaired.
vi	Oral	800 mg/day from week 36–41	HSV genital	M	41	Respiratory distress secondary to congenital lobar emphysema.
vii	Oral	800 mg/day from week 39–41	HSV genital	M	41	Fused digits of right hand.

among males compared to females (Jedd et al., 1988; Applegate and Druschel, 1995; Honein et al., 1999b), and two to three times higher in white infants compared to those of other races. In one population-based survey (Jedd et al., 1988), the rate of pyloric stenosis among males in 1980–1984 was 0.6%, so our findings should not be a cause for alarm.

The cooperation of government agencies, academic institutions, and the pharmaceutical industry in the design and operation of this registry was a novel approach that should be used more often; a registry for prenatal exposure to antiretroviral drugs is currently using this same methodology. The value of drug exposure registries has been reviewed previously (Andrews and Tilson, 1988; Reiff-Eldridge et al., 2000). Data from this acyclovir registry were reviewed during the FDA reclassification of acyclovir from Category C to B in 1995, and were especially helpful during the revision of the CDC STD treatment guidelines. The 1998 guidelines (CDC, 1998b) recommended treatment of first episodes of genital herpes as an option for pregnant women, whereas in the past, acyclovir treatment during pregnancy was recommended only in life-threatening situations (CDC, 1989, 1993b). Current guidelines (CDC, 2002) now also include a recommendation for treatment of severe recurrences in pregnant women.

The Registry's Advisory Committee determined that collection of additional information would be unlikely to substantially add to the existing knowledge about prenatal risk from acyclovir. The Acyclovir Pregnancy Registry was closed to new registrations in June 1998, after 14 years of data collection. The Acyclovir Pregnancy Registry Final Study Report was issued in October 1999; summaries are available by calling GlaxoSmithKline at 1-888-TALK2GW. Health care providers are encouraged to continue to report Zovirax and Valtrex exposures to the GlaxoSmithKline Global Clinical Safety and Pharmacovigilance Department (1-888-825-5249).

Acyclovir use in pregnancy has been reviewed previously (Brown and Baker, 1989). Acyclovir use among pregnant women is likely to increase, in the attempt to prevent neonatal herpes or to prevent cesarean deliveries. Cesarean delivery is currently recommended (Prober et al., 1992; ACOG, 1999; CDC, 2002; AAP, 2003) for women with signs or symptoms of genital herpes at the time of labor. Although risk of neonatal transmission is low among women with recurrent genital herpes (Brown et al., 1987, 1997, 2003), and cesarean deliveries do not always prevent neonatal herpes (Whitley et al., 1988; Stone et al., 1989), this recommendation is supported by a recent large cohort study that documented the protective effect of cesarean delivery (Brown et al., 2003). Antiviral therapy for pregnant women with genital herpes has been proposed as a strategy to prevent vertical transmission and also to decrease cesarean deliveries (Scott et al., 1996, 2002; Brown et al., 1997, 2003; Scott and Alexander, 1998; ACOG, 1999); however, this remains controversial. A recent clinical trial showed that daily suppressive use of acyclovir starting at 36 weeks gestation decreased frequency of clinical recurrences at delivery but had no effect on subclinical shedding or frequency of cesarean delivery (Scott et al., 2002). Another approach is to restrict cesarean deliveries to women with first episodes of genital herpes, rather than recurrences (Randolph et al., 1993); this approach is more cost-effective; moreover, reduced rates of cesarean sections are

not likely to result in increased rates of neonatal herpes (Gutierrez et al., 1999). Our study, while not specifically designed to address the effectiveness or broad safety of acyclovir when used in late pregnancy, did not identify any safety signals among the 288 cases involving third trimester exposure. The Acyclovir in Pregnancy Registry Committee recommends following the guidance in the CDC STD Treatment Guidelines (CDC, 2002), which are updated periodically.

This pregnancy follow-up study provides one of the largest studies of women exposed to any medication during pregnancy. Information collected over a 15-year period suggests that the birth defects experienced following antenatal exposure to acyclovir did not differ in overall rate or type from that observed in the general population.

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