Primary Maternal Herpes Simplex Virus-1 Gingivostomatitis During Pregnancy and Neonatal Herpes: Case Series and Literature Review

Sara A. Healy,1 Kathleen M. Mohan,1 Ann J. Melvin,1 and Anna Wald2
1Department of Pediatrics, Division of Pediatric Infectious Diseases, University of Washington, and Seattle Children’s Hospital and Research Institute, and 2Department of Medicine, Division of Infectious Diseases, Department of Epidemiology and Laboratory Medicine, University of Washington, and Vaccine and Infectious Diseases Institute, Fred Hutchinson Cancer Research Center, Seattle, Washington

Corresponding Author: Sara Healy, Seattle Children's Hospital, 4800 Sand Point Way NE, Seattle, WA 98105. E-mail: sara.healy@seattlechildrens.org.
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Background. Neonatal herpes simplex virus (HSV) is a serious, life-threatening infection that is usually acquired during birth from contact with infected maternal genital secretions. Primary maternal HSV gingivostomatitis is a rare occurrence during pregnancy, and HSV type 1 (HSV-1) neonatal disease after primary maternal HSV gingivostomatitis during pregnancy has not been reported in detail.

Methods. We reviewed the medical records of neonates (<28 days of age) with a confirmed diagnosis of neonatal HSV-1 at a single pediatric center from January 1981 to January 2010 to identify cases in which the mother had primary gingivostomatitis during pregnancy or at term.

Results. Seven neonates whose mothers had primary HSV-1 gingivostomatitis during pregnancy were identified from a review of 48 neonates with laboratory-proven HSV-1 neonatal disease. Of the 7 women, 2 presented with symptoms of primary HSV-1 gingivostomatitis during the first trimester and 5 in the third trimester. Three of the neonates developed skin, eye, and mucous membrane disease, 2 developed central nervous system disease, and 2 developed disseminated disease. One of the neonates with disseminated HSV-1 disease died.

Conclusions. Primary maternal HSV gingivostomatitis during pregnancy may lead to HSV-1 transmission to the neonate. Physicians caring for pregnant women should communicate the diagnosis of HSV gingivostomatitis to the neonate’s primary provider to ensure proper surveillance, early evaluation, and prompt treatment.

Neonatal herpes simplex virus (HSV) has long been recognized as a devastating consequence of maternal HSV type 1 (HSV-1) and HSV type 2 (HSV-2) genital infections [1, 2]. Although recurrent genital HSV infection is the most common manifestation of HSV during pregnancy, women who have a primary genital HSV infection at term are at the greatest risk of transmitting the virus to their neonate [3–7]. However, limited information has been published on the management and outcomes of neonates born to women with primary HSV-1 gingivostomatitis during the course of their pregnancy, and specifically late in the third trimester.

We present a case series of 7 neonates who were evaluated and treated for neonatal HSV-1 infection at a single institution in a 29-year period with a maternal history consistent with primary HSV-1 gingivostomatitis during pregnancy or in the immediate postnatal period.

CASE REPORT

A 10-day-old boy born at 39 weeks gestational age was admitted to Seattle Children’s Hospital for decreased oral intake, lethargy, emesis, hypothermia, hypoxia, diarrhea, and mottling for 2 days. An erythematous patch on his abdomen without any associated vesicular or pustular lesions was noted for the last 4–5 days.

Maternal history was notable for fever, diffuse myalgias, arthralgias, and bilateral tender cervical lymphadenopathy 2 days before delivery. Within 24 hours of delivery, the mother developed a pustular lesion in her
posterior oropharynx and multiple vesicular lesions along her right vermilion border. She was diagnosed with HSV gingivostomatitis and was empirically started on valacyclovir 3 days postpartum, and resolution of all symptoms and lesions occurred within 2 days. Before this illness, the patient’s mother had no history of oral or genital lesions or symptoms suggestive of HSV. Her partner had a history of recurrent oral herpetic lesions, but no recent outbreaks and no history of genital lesions.

On admission, a physical examination revealed a mottled, but in no acute distress neonate with hypothesmia, tachypnea, and hypoxia. The abdomen was soft, nondistended with mild tenderness to palpation in the right upper quadrant. The liver edge was palpable. Skin examination was appreciable for multiple erythematous papular lesions on the chest and abdomen and a vesicular lesion on the thigh.

Laboratory evaluation showed a white blood cell count of 5700/mm³ with an absolute lymphocyte count of 1881/mm³ and platelet count of 139,000/mm³. The patient’s aspartate aminotransferase was 7073 units/L, alanine transaminase was 2721 units/L, γ-glutamyl transferase was 290 units/L, prothrombin time was 38.0 seconds, international normalized ratio was 1.4, activated partial thromboplastin time was 79 seconds, and fibrinogen was <40 mg/dL. All bacterial cultures, including blood, urine, and cerebrospinal fluid (CSF), showed no growth. CSF studies, including white blood cell count and protein concentration, were normal. Additional viral studies, including respiratory viral fluorescent antibody and enterovirus and parechovirus polymerase chain reaction (PCR) on the CSF, were negative. HSV surface cultures, including skin lesions, nasopharyngeal, and rectal cultures, were all positive for HSV-1. Initial HSV serum PCR was 57,000,000 copies/mL and was CSF HSV PCR negative. After his initial evaluation, the patient was empirically started on ampicillin, gentamicin, and acyclovir.

The patient received acyclovir (20 mg/kg per dose intravenously every 8 hours) for disseminated HSV infection. He also developed an increasing oxygen requirement, disseminated intravascular coagulopathy, and significant transaminitis, resulting in the need for multiple transfusions of fresh frozen plasma, cryoprecipitate, and platelets. Although not an established standard of care, because the patient had a persistently positive serum HSV PCR, he received 43 days of acyclovir until his serum PCR was negative. The patient was discharged on day of life 33 with a peripheral intravenous central catheter to complete intravenous acyclovir at home. Neurological and developmental assessment at 1 year of age was normal.

PATIENTS AND METHODS

We performed a retrospective review of the medical records of neonates (≤28 days of age) with the diagnosis of neonatal HSV-1 at Seattle Children’s Hospital from January 1981 to January 2010. Neonates were classified as having HSV skin, eye, and/or mucous membrane (SEM) disease, central nervous system disease (CNS), or disseminated disease [7].

Diagnosis of maternal primary HSV-1 gingivostomatitis was determined using the following criteria: (1) no previous diagnosis or clinical history of HSV-1 or HSV-2 oral or genital infection; (2) negative maternal or neonatal HSV (HSV-1 and HSV-2) serological testing at the time of diagnosis, or recent negative maternal HSV (HSV-1 and HSV-2) serological testing preceding maternal symptoms; and (3) maternal clinical history of symptoms consistent with primary HSV gingivostomatitis infection, including at minimal oral ulcerations and swollen gums with or without additional fever, lymphadenopathy, and/or pharyngitis that occurred during the course of the pregnancy or ≤72 hours after delivery.

Using standardized forms, we extracted maternal information, including demographic data, obstetrical history, systemic symptoms and diagnostic evaluation, and postpartum history. Likewise, information on the neonate (including presenting symptoms and medical evaluation, diagnostic tests, hospital course, consultations, complications, and outpatient follow-up) was reviewed and extracted. The study was approved by the Institutional Review Board of Seattle Children’s Hospital.

A review of the literature was conducted using the key words “HSV,” “neonatal HSV,” and “HSV gingivostomatitis.” Five publications were identified that presented data consistent with the diagnosis of primary maternal HSV-1 gingivostomatitis during pregnancy. The references cited in these publications were also cross-referenced and reviewed in attempt to identify any additional case reports or series of primary maternal HSV-1 gingivostomatitis during pregnancy that may have been missed in the primary search.

RESULTS

We identified 48 neonates with laboratory-documented HSV-1 infection evaluated at our institution between January 1981 and January 2010. Of these 48 neonates, 31 (65%) cases were excluded because the mother had a clinical history or laboratory evidence consistent with HSV-1 reactivation (n = 12) or insufficient information was available for a definitive diagnosis of primary HSV-1 in the mother.
Seven (35%) neonates were identified with maternal or neonatal viral detection tests (HSV culture, PCR), antibody studies (immunoglobulin [Ig]G, IgM, Western blot), and clinical history consistent with primary maternal HSV-1 infection during pregnancy. Of those 17 women, 2 (12%) had genital lesions at the time of diagnosis, 2 (12%) had clinical history and viral culture results consistent with primary HSV-1 mastitis, and 6 (35%) had no maternal symptoms at all. Seven (41%) of the mothers had a maternal history consistent with primary HSV-1 gingivostomatitis. No cases of HSV-2 primary maternal gingivostomatitis were identified in the defined search period. A summary of the 7 identified neonates is provided in Table 1.

The median maternal age at delivery was 26 years (range, 24–34 years) and the median gestational age was 39 weeks (range, 33–40 weeks). Four of the 7 neonates were born via vaginal delivery; in 5 (71%) neonates, pregnancy complications were noted, including preterm labor (n = 1), preterm prolonged rupture of membranes (n = 1), prolonged rupture of membranes (n = 1), group B streptococcal colonization (n = 1), use of forceps (n = 1), vacuum-assisted delivery (n = 1), or maternal fever (n = 4). None of the neonates had a scalp electrode placed during delivery, although this information was only available for 3 of the 7 neonates. None of the mothers had genital lesions or genital symptoms or evidence of mastitis noted during pregnancy, at delivery, or postpartum.

Two (29%) mothers presented with symptoms of primary HSV-1 gingivostomatitis during the first trimester, none (0%) during the second trimester, and 5 (71%) during the third trimester. Three (60%) of the 5 women who presented in the third trimester had documented oral lesions at the time of delivery, and, of those 3, only 1 was treated with antiviral medications for HSV during the postpartum period. One (14%) of the 7 neonates was a girl. The median age of onset of first symptoms was 5 days (range, 4–9 days). All but 1 neonate presented with skin lesions, and HSV-1 was detected in the lesions in 4 of these 6 neonates. Additional initial symptoms included conjunctivitis in 2 (29%) of 7; only 1 of 7 (14%) had a fever at presentation. None of the 7 neonates had oral lesions. Three (43%) of the 7 neonates were diagnosed with SEM disease, 2 (29%) were diagnosed CNS disease, and 2 (29%) were diagnosed disseminated disease. One neonate with disseminated disease died.

Four (57%) of the 7 neonates, including 3 neonates with skin lesions present at the time of evaluation, were seen by a physician before the visit that resulted in the diagnosis of HSV-1, resulting in a delay in receipt of antiviral treatment in 3 (75%) of 4 by 1–2 days due to lack of initial evaluation for HSV.

All neonates had at least 2 samples sent for viral identification, and a median of 2 samples were positive for HSV-1. HSV-1 was identified in the skin of 4 (57%) of 7 patients and in the nasopharynx of 4 (57%) of the 7 patients. Three neonates had plasma sent for HSV PCR, and 2 were positive with initial levels of 120 000 and 57 000 000 copies/mL, respectively. HSV was not detected in the CSF of any of the neonates, although spinal fluid was assayed with PCR in only 5 (71%) of the 7 neonates. For the 2 neonates who were diagnosed with CNS involvement and had pleocytosis and proteinosis, PCR was not available for diagnostic use at that time, and the viral cultures were negative. None of the samples were positive for HSV-2.

The duration of treatment with antiviral therapy (vidarabine [n = 2] and acyclovir [n = 5]) ranged from 10 to 43 days (median, 11 days), and length of hospital stay varied from 3 to 35 days (median, 13 days).

Of the 5 neonates who underwent formal ophthalmological evaluation at presentation, 3 (60%) had abnormal exams consistent with HSV retinitis. These 3 neonates also had clinical conjunctivitis at their initial presentation. In-patient hearing test results were only available for 2 of the neonates and were normal. Neurological imaging (head computed tomography or magnetic resonance imaging) was obtained on 6 (86%) of the 7 neonates during their initial hospitalization. Three (50%) of the 6 neonates had abnormal imaging, including the 2 diagnosed with HSV-1 CNS disease and the neonate that died secondary to disseminated HSV. Neurological outcomes through at least 6 months of age were available for 5 of the neonates and were noted to be normal in 4 (80%) of the neonates, including 1 of the neonates with CNS disease. One of the 2 neonates classified as CNS HSV with documented abnormal neurological imaging was found to have mild deficits in expressive/receptive language skills, fine finger skills, and perceptual ability when evaluated at 2 years of age. Three (50%) of the 6 surviving neonates developed skin recurrences within 6 months of initial diagnosis.

One of the mothers who acquired primary maternal HSV-1 gingivostomatitis late in the third trimester was noted to have HSV-1 DNA present in her blood 48 hours postpartum upon follow-up testing of a stored sample. No additional maternal blood samples or genital samples were sent for HSV PCR analysis at the time of diagnosis or in follow-up.
<table>
<thead>
<tr>
<th>Sex of Neonate</th>
<th>Maternal Age</th>
<th>Type of Delivery</th>
<th>Trimester of Symptoms</th>
<th>Maternal Clinical Features</th>
<th>Maternal Symptom(s) at Delivery</th>
<th>Age of 1st Symptoms (Days)</th>
<th>Neonate Clinical Features</th>
<th>Diagnostic Testing</th>
<th>HSV Syndrome</th>
<th>Duration of Treatment (Days)</th>
<th>Outcome</th>
<th>Recurrence</th>
</tr>
</thead>
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<tr>
<td>F&lt;sup&gt;b&lt;/sup&gt;</td>
<td>33</td>
<td>C/S</td>
<td>1st</td>
<td>Gingivostomatitis</td>
<td>No</td>
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<td>Skin lesion, conjunctivitis</td>
<td>Maternal: WB</td>
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<td>10</td>
<td>Alive</td>
<td>No</td>
</tr>
<tr>
<td>M&lt;sup&gt;b&lt;/sup&gt;</td>
<td>26</td>
<td>Vaginal</td>
<td>1st</td>
<td>Gingivostomatitis, pharyngitis</td>
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<td>4</td>
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<td>Maternal: WB</td>
<td>CNS</td>
<td>10</td>
<td>Alive</td>
<td>Yes</td>
</tr>
<tr>
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<td>3rd</td>
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<td>Yes</td>
<td>7</td>
<td>Skin lesion, conjunctivitis</td>
<td>Maternal: WB</td>
<td>SEM</td>
<td>10</td>
<td>Alive</td>
<td>Yes</td>
</tr>
<tr>
<td>M</td>
<td>24</td>
<td>C/S</td>
<td>3rd</td>
<td>Fever, oral ulcerations, adenopathy</td>
<td>No</td>
<td>4</td>
<td>Fever, tachypnea, jaundice, bradycardia</td>
<td>Maternal: WB</td>
<td>Disseminated</td>
<td>11</td>
<td>Died</td>
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<tr>
<td>M</td>
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<td>Vaginal</td>
<td>3rd</td>
<td>Gingivostomatitis</td>
<td>No</td>
<td>9</td>
<td>Skin lesion, conjunctivitis</td>
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<td>14</td>
<td>Alive</td>
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<td>M</td>
<td>34</td>
<td>C/S</td>
<td>3rd</td>
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<td>Skin lesion</td>
<td>Maternal: WB</td>
<td>SEM</td>
<td>15</td>
<td>Alive</td>
<td>Yes</td>
</tr>
<tr>
<td>M</td>
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<td>Vaginal</td>
<td>3rd</td>
<td>Gingivostomatitis, pharyngitis, swollen gums, adenopathy, myalgias, arthralgias, fever</td>
<td>Yes&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6</td>
<td>Skin lesion, hypothermia, hypoxia, lethargy, diarrhea, emesis</td>
<td>Maternal: WB</td>
<td>Disseminated</td>
<td>43&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Alive</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous system disease; C/S, caesarean section; Cx, culture; HSV, herpes simplex; virus; Neg, negative; F, female; FA, fluorescent antibody; M, male; N/A, not applicable; PCR, polymerase chain reaction; SEM, skin, eye, mucous membrane disease; Unk, unknown; WB, Western blot.

<sup>a</sup>Antiviral treatment varied based on year of diagnosis, but includes vidarabine and acyclovir. CNS cases treated for 10 days occurred before current recommendations of 21 days.

<sup>b</sup>These 2 cases were previously reported by Brown et al [1].

<sup>c</sup>Valacyclovir given to mother after delivery.

<sup>d</sup>Although not an established standard of care, this patient received a prolonged course of acyclovir secondary to persistently positive serum HSV-1 PCR.
A review of the literature of clinical outcomes of neonates born to mothers with documented primary HSV gingivostomatitis during pregnancy or at the time of delivery is limited to a few case reports, as summarized in Table 2 [1, 8–11]. In contrast to our case series, no adverse neonatal outcome was noted in the previously reported cases.

**DISCUSSION**

We report 7 cases of neonatal HSV-1 infection in neonates born to women with primary HSV-1 gingivostomatitis during pregnancy, including 5 with diagnosis at term or within 72 hours postpartum. To our knowledge, this is the first detailed report of neonatal HSV infection in this setting.

The mechanism by which neonates acquire HSV infection during primary maternal HSV-1 gingivostomatitis is unclear. Most neonates become infected with HSV-1 or HSV-2 during birth through exposure to infected genital secretions, although occasional intrauterine infection has been reported [2, 12]. In addition, approximately 10% of infants with HSV-1 are infected after birth, presumably from oral shedding from close contacts [2]. In our cases, all 3 routes could have resulted in transmission.

In the neonates whose mothers presented with symptoms at the time of delivery, direct transmission of HSV-1 from the mother to the neonate via hematogenous spread is a potential mechanism of acquisition. Studies of immunocompetent adults, pregnant women, and children have shown that viremia occurs in individuals with primary HSV infection, including primary HSV-1 gingivostomatitis [13, 14]. In a single instance, as described previously, 1 of the mothers who acquired primary maternal HSV-1 gingivostomatitis late in the third trimester was noted to have detectable levels of HSV-1, via PCR, in her blood 48 hours postpartum, which supports this possible mechanism of transmission.

Transmission during the postnatal period of HSV-1 via mucosal exposure has been reported in the literature [15–18]. In at least 1 neonate reported above, the initial vesicular lesion appeared at the site of trauma from vacuum placement during the delivery, which implies the possibility of an indirect mode of transmission from saliva or genital secretions to an open skin wound. Yet another neonate presented without any skin lesions but was noted to have detectable virus in his nasopharynx. Previous studies have noted that HSV can concurrently be detected in the saliva or oral mucosa and anogenital secretions in persons who have asymptomatic viral shedding [19–22]. In adults, HSV can be concurrently in the oropharyngeal cavity and genital areas after a primary genital outbreak [22, 23]. In a study of 12 children, it was noted that during primary gingivostomatitis infection, HSV could be detected in the children’s stools or mouth for an average of 23 days; however, for these children, the virus was not detected in the stool before being detected in the mouth, and investigators concluded that the presence of HSV in the stool was derived from the oropharynx [24]. However, we have not found reports of persons with HSV gingivostomatitis who had an evaluation of genital secretions for the presence of HSV at the same time. In contrast, primary genital HSV-1 infection is accompanied by oral HSV-1 shedding in approximately 70% of cases.

Our data contradict prior reports that have indicated that primary maternal HSV-1 gingivostomatitis during

<table>
<thead>
<tr>
<th>Year, Publication*</th>
<th>Number of Cases</th>
<th>Trimester of Symptoms</th>
<th>Maternal Diagnosis</th>
<th>Neonatal Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case 1</td>
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<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Case 2</td>
<td>2nd</td>
<td>Culture, clinical</td>
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<td></td>
<td>Case 3</td>
<td>2nd</td>
<td>Culture, clinical</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Case 1</td>
<td>2nd</td>
<td>Culture, clinical</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Case 2</td>
<td>3rd</td>
<td>Culture, clinical</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Case 3</td>
<td>3rd</td>
<td>Culture, serology, clinical</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Case 4</td>
<td>2nd</td>
<td>Serology, clinical</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Case 2</td>
<td>2nd</td>
<td>PCR, clinical</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous system disease; PCR, polymerase chain reaction.  
*Two cases from Brown et al [1] were not included in literature review because the reported cases are described in detail in Table 1.  
bNormal is defined as no neonatal complications attributed to HSV exposure and no evidence of HSV infection and/or disease.  
cUnderwent therapeutic abortion with noted hypoplastic right hemicerebrum malformation that the authors assume was unrelated to the maternal infection; no viral studies were obtained.
pregnancy is not associated with adverse neonatal outcomes [1, 7–10]. Our case series is limited by lack of prospectively and systematically collected data and lack of information regarding the total number of cases of maternal primary HSV-1 gingivostomatitis (denominator) during the study period.

Currently, the optimal approach to an asymptomatic neonate with known exposure to HSV at birth is unclear. The American Academy of Pediatrics recommends following neonates born to mothers who have a known exposure, such as active genital lesions at term, with surface cultures at 12 to 24 hours of life in conjunction with close follow-up to assess the infant for signs of illness and to initiate systemic therapy [25]. This approach is used so that neonates are identified early and undergo early initiation of therapy, which has been shown to be strongly associated with favorable outcomes. In instances of exposure to known primary genital infections, the Red Book recommends consideration of empiric parenteral acyclovir treatment [25]. However, an asymptomatic primary exposure is usually not identified, and routine testing of the mother at time of delivery is not done. In addition, no recommendations address the management of neonates born to women with HSV gingivostomatitis. The common-sense approach, including counseling mothers about good hand hygiene, wearing a disposable surgical mask when touching the neonate, and refraining from kissing or nuzzling the neonate until the lesions have dried and crusted over, is of uncertain utility, especially if the exposure occurs during birth [6].

CONCLUSIONS

Clinical trials have been largely limited to addressing genital HSV and efficacy and safety of antiviral prophylaxis in mothers who were identified with recurrent or primary infection during the pregnancy and with clinical-management guidelines published by the American College of Obstetrics and Gynecologists [26]. Although these current guidelines have beneficial treatment tools, their impact on prevention of neonatal HSV infection is limited.

Currently, there are no published data on the benefits of antiviral therapy on affecting neonatal outcomes or decreasing the incidence of viremia or degree of viral shedding in pregnant women with primary HSV-1 gingivostomatitis. In addition, all previous case reports and series published up until now have indicated that primary maternal HSV-1 gingivostomatitis during pregnancy is not associated with adverse neonatal outcomes [1, 7–10]. However, given the identified adverse neonatal outcomes seen in our review, treating physicians should apply close monitoring practices and have a low threshold for prompt evaluation and treatment of these at-risk neonates. Further applications of recommendations to this rare group of mothers, such as indications for caesarean section and antiviral therapy during pregnancy, will require additional collaborative research.

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