CASE REPORT

# Intrauterine Acquired Congenital Herpes Simplex Virus Infection in a Newborn

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## Abstract

**Aim:** We present a fatal case of congenital herpes simplex virus (HSV) infection following exposure of a non-immune mother by her partner during critical fetal development.

**Background:** Globally, neonatal HSV infection affects 1 in 10,000 births. The most common mode of transmission is perinatally through passage through the vaginal canal (85%), followed by postnatal acquisition (10%). Rarely, intrauterine infection can occur (5%) resulting in congenital HSV, presenting with a classic triad of skin desquamation, chorioretinitis and brain malformations including hydrocephaly, anencephaly, and porencephaly.

**Case description:** A 30-week pregnant woman with a history of flu-like illness at 18 weeks presented with decreased fetal movement and vaginal bleeding. Initial evaluation showed echogenic bowel on ultrasound. At 30 weeks, polyhydramnios and fetal brain abnormalities were noted. A c-section was performed, and the infant required resuscitation. The infant's father reported a history of genital HSV outbreaks and HSV-2 was detected in the infant's blood. The infant had extensive skin desquamation, seizures, and succumbed to fatal brain malformations.

**Conclusion:** While maternal treatment with antiviral medication and cesarean section are effective in preventing perinatal HSV infection, congenital infection in the first or second trimester of pregnancy with devastating consequences for the fetus can occur in women without HSV immunity.

**Clinical significance:** Given the lack of available HSV immunization, protection of non-immune pregnant individuals from HSV exposure is currently the only preventive measure against congenital HSV disease.

**Keywords:** Brain malformation, Case report, Congenital infection, Herpes simplex virus, Newborn, Prevention.

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## Background

Herpes simplex virus (HSV) is a ubiquitous virus with an estimated global prevalence of 66% for the HSV-1 and 13% for the HSV-2 serotype.[1,2] Both serotypes can cause genital infection and have been implicated in neonatal HSV disease. Neonatal HSV can occur from either primary infection during pregnancy (25–60% risk of transmission), or rarely from an outbreak in a mother with a history of recurrent genital lesions (<2%).[3] Although both serotypes can cause neonatal HSV, serotype 2 has been linked to worse central nervous system (CNS) disease in infants.[4–6] Maternal diagnosis can be challenging since up to 80% of women are asymptomatic,[7] which delays treatment until the infant is recognized to be affected. Here we present a challenging case of an infant with rare intrauterine HSV-2 infection resulting in severe neonatal disease.

## Case Description

A pregnant woman presented at 30 weeks gestation with decreased fetal movement, vaginal bleeding, and contractions. Pregnancy was notable for a flu-like illness at 18 weeks gestation with associated dysuria and incontinence. During that time, she passed a thick clump of mucousy blood-tinged discharge. A cervical exam was significant for a friable cervix with yellow frothy discharge. Urine culture was negative. Wet prep contained polymorphonucleated cells but otherwise unrevealing. Ten days following evaluation for the illness at 18 weeks, fetal ultrasound was notable for echogenic bowel with no other noted anomalies (Fig. 1). A standard HSV IgG laboratory panel revealed the presence of HSV-2 IgG [9.49 gm/L (normal 0.00–0.90)] but no HSV-1 IgG [<0.91 gm/L (normal 0.00–0.90)]. No testing for HSV IgM was performed. Given isolated echogenic bowel findings, she was recommended to have a routine follow-up with her obstetrician.

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**Patient consent statement:** The author(s) have obtained written informed consent from the patient for publication of the case report details and related images.

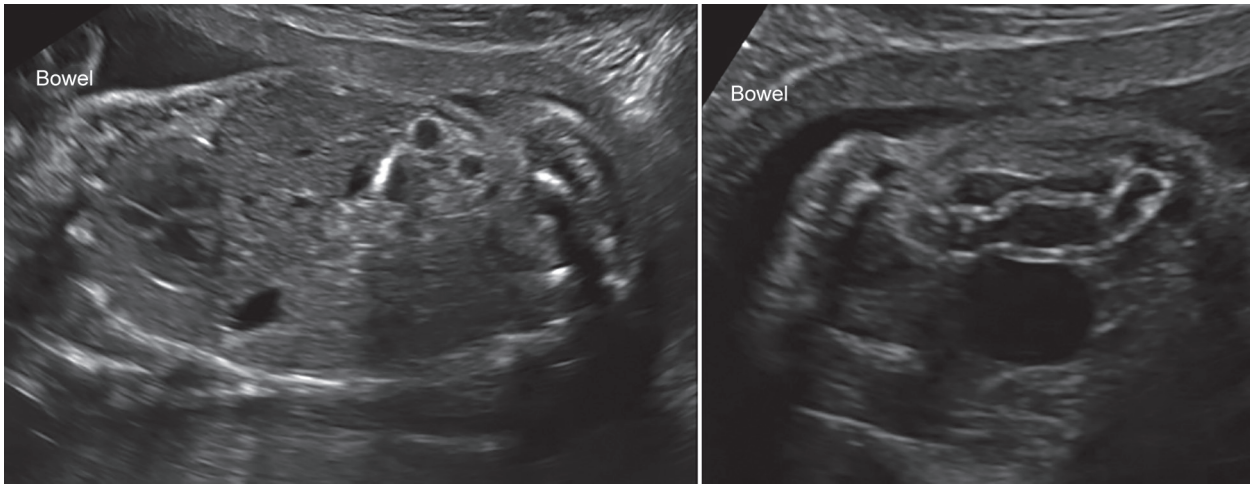


**Fig. 1:** Prenatal ultrasound showing portions of the fetal bowel to appear echogenic and fluid-filled. There are no signs of overt dilation, with the widest diameter measuring 6 mm (normal <7 mm)

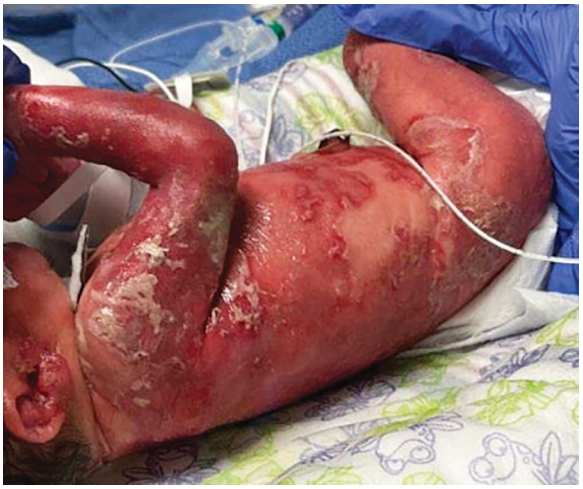

**Fig. 2:** Extensive desquamation and excoriation of right upper extremity and torso

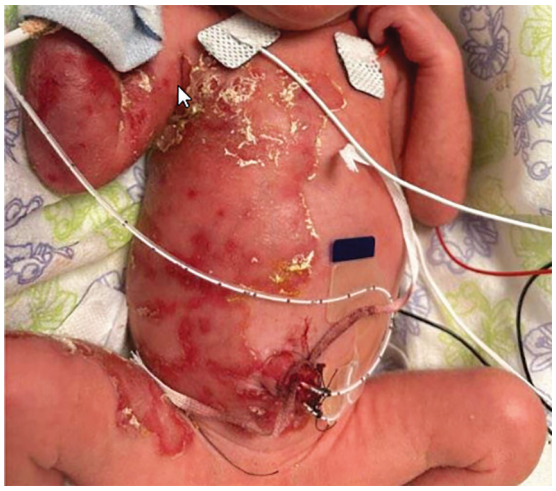

**Fig. 3:** Erythematous erosions and scarred thin plaques with some overlying crust in a dermatomal distribution along unilateral chest and trunk

On the day of the presentation, fetal ultrasound showed new findings of severely dilated 3rd and 4th ventricles, polyhydramnios, and a category II fetal heart rate tracing. Given these findings and a breech presentation, c-section was performed. At birth, the infant had poor tone with no respiratory effort. She was resuscitated following Neonatal Resuscitation Program (NRP) guidelines and intubated for apnea. Physical exam was significant for extensive skin desquamation involving the right arm, face, and torso (Figs 2 and 3). Her birth weight was 1,415 gm (60.9%, $Z = 0.28$), her head circumference 27.2 cm (50.1%, $Z = 0.08$), and her length 39.5 cm (62.8%, $Z = 0.33$).

Shortly after admission to the Neonatal Intensive Care Unit (NICU), the father of the infant provided a history of recurrent genital HSV outbreaks, with an episode shortly before the maternal febrile illness at 18 weeks of pregnancy. Polymerase chain reaction (PCR) testing of the infant detected HSV-2 from surface swabs of a skin lesion, the eyes, and blood. Toxoplasmosis IgG and IgM antibodies were negative, as was blood PCR for cytomegalovirus (CMV). The bacterial and fungal blood cultures showed no growth. Treponemal IgG was negative. Complete blood count was significant for thrombocytopenia to a nadir of $65 \times 10^3$ mc/L and C-reactive protein was 2.6 mg/L (0.3–6.1 mg/L).

Given the desquamating appearance of the rash, the differential diagnosis included epidermolysis bullosa or bullous pemphigoid, although this was moved lower on the differential once it was appreciated that the lesions did not extend from skin trauma. An infectious etiology such as disseminated candidiasis was considered especially with white demarcation of plaques. Infections, such as CMV, toxoplasmosis, rubella, syphilis, parvovirus, and HSV were considered in the setting of prenatal brain malformation.

Prompt treatment with ampicillin, gentamycin, acyclovir, and fluconazole was started. Subspecialty involvement of

Dermatology recommended sterile water baths and generous use of emollients. Ophthalmologic evaluation was significant for bilateral acute retinal necrosis without retinal detachment, as well as corneal dendrites on the right (Fig. 4) and corneal abrasion on the left. The patient was started on artificial tears, ganciclovir, and moxifloxacin eye drops. Shortly after admission to the NICU, the patient developed right arm rhythmic jerking concerning seizures. She was placed on continuous electroencephalogram (EEG) which confirmed seizure activity and an abnormal background consistent with lack of cortical electrical activity except for ictal events. A head ultrasound revealed poor differentiation between gray and white matter, ventriculomegaly of the lateral and third ventricles with effacement of the fourth ventricle, an absent corpus callosum, punctate foci of echogenicity near the left vertex concerning ischemia vs hemorrhage, a cystic structure in the posterior fossa with mass effect on an atrophic appearing cerebellum, and diffuse periventricular echogenicity (Fig. 5). Given all these findings and severe neurologic prognosis, her parents made the loving choice of redirecting her care and allowed natural death.

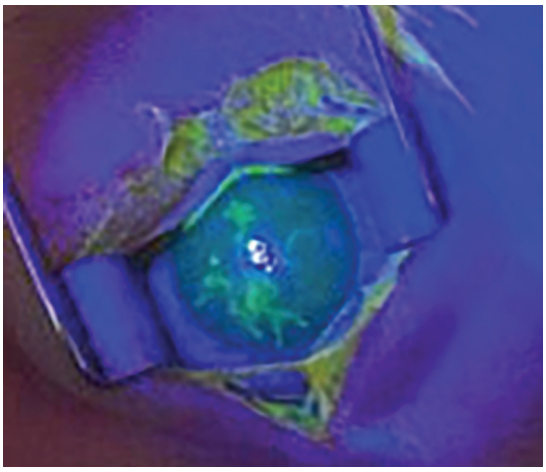

**Fig. 4:** Fluorescein staining of right eye showing large dendritic lesion

## Discussion

Although rare, in utero HSV transmission can present with severe devastating consequences for the fetus as demonstrated here. Thirty percent of in utero infections occur in the first trimester, 30% in the second, and 40% in the third.[8] In a literature review by Fa et al. of 36 congenital HSV cases, the most common postnatally observed manifestations are skin desquamation, chorioretinitis, and hydrocephaly, which were all features of this case.[9] Neonatal skin findings are heterogenous and include erosions, plaques, erythematous patches, or ulcerations. Atrophic scars and aplasia of the skin have been described and despite the neurotrophic characteristics of the virus, dermatomal distribution of the skin lesions is uncommon.[10]

Prenatal recognition of HSV infections can be challenging. Maternal primary genital HSV-2 infection can present with a febrile illness and flu-like symptoms along with vaginal or cervical lesions,[9] but over 80% of women are asymptomatic.[8] Thus, most cases of neonatal herpes occur in mother–infant dyads in which the mother is undiagnosed.[8,11,12] Prenatal ultrasound findings of congenital herpes infection involve primarily the CNS and are non-specific, creating a broad differential diagnosis. The CNS abnormalities associated with congenital HSV include ventriculomegaly, hydrocephaly, agenesis of the corpus callosum, porencephaly, intracranial calcifications, cerebral hemorrhage, microcephaly, and microphthalmia.[9] Herpes simplex virus-2 has been observed to present with more severe CNS findings compared with HSV-1.[3] The risk of transmission to the fetus or newborn is much greater with a primary genital infection during pregnancy compared with reactivation of infection (25–50 vs 1%),[11] although congenital HSV-1 has been reported in mothers with primary gingivostomatitis febrile illness.[3,13] Up to 50% of cases of neonatal HSV are due to the HSV-1 serotype, with 75% of those associated with recently acquired genital HSV-1.

Fetal HSV transmission resulting in congenital HSV infection is thought to occur from maternal viremia and passage through the placenta. Placental pathology in this case showed negative staining for the herpes virus. This is likely due to the temporary shedding of the virus during the acute illness, which again highlights the high index of suspicion needed for the correct diagnosis and treatment of HSV infections. Placental pathology was significant

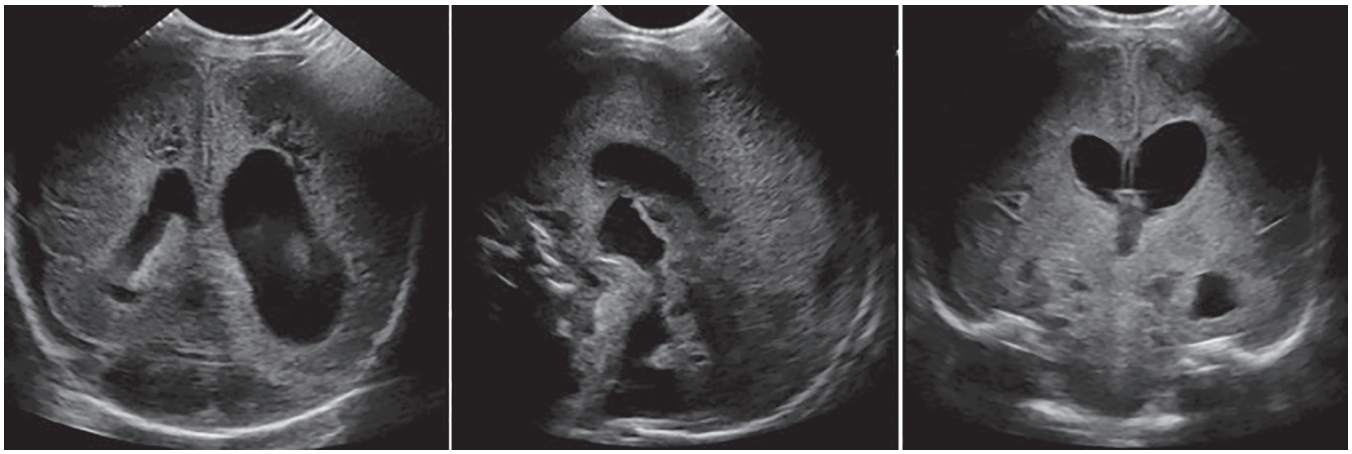

**Fig. 5:** Head ultrasound images showing poor differentiation between gray and white matter, ventriculomegaly of the lateral and third ventricles, an absent corpus callosum, punctate foci of echogenicity near the left vertex concerning for ischemia versus hemorrhage, and a malformed cerebellum.

for accelerated villous maturation, a three-vessel cord with acute vasculitis, organizing intervillous hematoma, and multifocal villous edema, which have all been described in the literature.[14] Infant postmortem autopsy was not performed per parental request.

Pregnancy may increase susceptibility to new infection. Prevention of primary infection during pregnancy currently includes barrier protection when sexual partners are known to be seropositive for HSV and treatment of the infected partner with daily valacyclovir. Condoms and valacyclovir each confer around a 50% rate of efficacy in the reduction of transmission of genital HSV. Measures taken to reduce congenital herpes include the administration of antivirals for women presenting with a primary HSV infection during pregnancy. Treatment at the time of diagnosis decreases viremia and transmission.[15] Antiviral therapy is also recommended for women at or beyond 36 weeks of gestation who are at risk for recurrent HSV infection. Cesarean delivery is recommended for women with active primary or secondary HSV lesions at the time of delivery.[16]

Universal screening with serologic testing in pregnancy has been proposed to identify the women at the highest risk for primary infection during pregnancy. Not only would this approach detect women at risk for infection, but it would identify women with existing asymptomatic infection at risk for viral shedding at delivery.

## Conclusion

Although rare, in utero HSV transmission can have devastating consequences for the fetus. While maternal treatment with antiviral medication and C-sections are effective in preventing perinatal HSV infection in the newborn, limited options currently exist to prevent congenital infection in the first or second trimester of pregnancy.

### Clinical Significance

While current research is underway to develop monoclonal antibody treatments to reduce recurrent infection and perinatal transmission,[17] vaccine development offers the most effective strategy to prevent or reduce herpes infections.[18] While prophylactic vaccines would need to be administered in early childhood, therapeutic vaccines could decrease shedding and reactivation of HSV in symptomatic and asymptomatic adults and therefore lower the infection risk for susceptible pregnant women.[2]

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