

A Case report: Maternal Sepsis During Pregnancy

Disseminated Herpes Simplex Virus

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A case of disseminated herpes simplex virus during the second trimester of pregnancy is reviewed. This is a rare complication of herpes simplex virus, but is a disease process that should be considered as part of the differential diagnosis with worsening maternal sepsis of unknown origin. Disseminated herpes simplex virus can present as pregnancy related medical conditions such as preeclampsia with severe features, HELLP syndrome, and acute fatty liver of pregnancy. It is important to recognize the possibility of disseminated herpes simplex virus early in the disease process plus being able to differentiate this from pregnancy related complications as all the above mentioned disease processes can have high maternal and neonatal mortality if not managed appropriately early in the disease process.

Introduction

Genital herpes infection occurs in one in five women in the United States. It is one of the most common sexually transmitted infections. In the United States HSV-1 is an important cause of genital herpes and is increasing in college students [1]. Approximately 45 million adolescents and adults in the United States are infected with HSV-2. Approximately 22% of pregnant women are infected with HSV-2, 10% are at risk of acquisition of genital HSV from their infected partners, and 2% of women acquire genital herpes during pregnancy [1]. Only approximately 5-15% of infected individuals report recognition of infection. Disseminated HSV remains rare in pregnancy [3]. Risk factors for HSV infection include female gender, duration of sexual activity, minority, ethnicity, previous genital infections, family income, cocaine abuse, and number of sex partners [1,6].

Recent findings reveal that first time infection of the mother is the most important factor for transmission of genital herpes from mother to fetus/newborn. Pregnant women who acquire genital herpes as a primary infection in the latter half of pregnancy, rather than prior to pregnancy, has the greatest risk of transmitting the virus to the newborn or of dissemination.

Disseminated herpes simplex virus can present clinically as encephalitis, hepatitis with or without central nervous system involvement, and disseminated skin lesions [1,2,4,6]. With liver involvement mortality is high. Flewett et al reported the first case of disseminated HSV infection in pregnancy in 1969. Less than one hundred cases have been reported since the initial case report by Flewett et al [3]. Since that time disseminated HSV still remains an uncommon diagnosis but as the incidence of herpes

simplex virus type-I and type-II increases in the population the diagnosis and earlier treatment of the disease needs to be higher on the clinical differential of obstetricians [6].

A case of disseminated HSV-2 that initially presented as maternal sepsis of unknown origin is reviewed. The herpes infection was recognized as the patient status deteriorated. With treatment initiation and suppressive therapy administered for the remainder of the pregnancy a successful pregnancy outcome for the mother and neonate occurred.

Case Report

A 35-year-old Gravida 3 Para 1011 intrauterine pregnancy at 21w6d gestation by patient report that presented with complaints of febrile illness with dysuria, urgency, frequency and bilateral lower back pain for 2 days. She denied any obstetric complaints at presentation. WBC was 10.4K with a left shift of 90.2 neutrophils, lactic acid within normal limits. Vital signs were significant for tachycardia and hypotension. She was subsequently admitted to the OB/GYN service after being administered Zosyn in the emergency department.

She was started on antibiotic therapy of Rocephin 1 gram q 12 hours for suspected pyelonephritis. Blood cultures and urine cultures were obtained prior to administration of antibiotics. The patient remained febrile, tachycardic, and hypotensive after admission to the general medicine floor and was subsequently transferred to the intensive care unit due to need for continued fluid resuscitation.

OB Complete ultrasound was performed upon admission to confirm gestational age due to patient receiving prenatal care from an outside provider and not having access to prenatal records at time of admission. A gestational age of 24 weeks and 4days of gestation was established versus patient's reported gestational age by LMP.

The patient remained febrile with cultures pending on hospital day 2. She started to complain of possible rupture of membranes due to leakage of clear fluid. Bedside sterile speculum exam with negative pooling, negative nitrazine, and negative ferning ruled out premature rupture of membranes. Patient status continued to deteriorate during hospital day 2 into hospital day 3 with complaints of shortness of breath and feelings of chest heaviness. The pulmonary service was consulted due to worsening oxygen saturation. Respiratory support was required with BiPap. Due to the large amount of intravenous fluids that was required to stabilize blood pressure Lasix was administered secondary to worsening pulmonary edema.

On hospital day 4 fever and tachycardia worsened as well as a new onset transaminitis was detected with complaint of worsening abdominal pain. A right upper quadrant ultrasound was found to be within normal limits. Blood pressures remained

normotensive to hypotensive. Additional laboratory workup performed with normal findings of fibrinogen, haptoglobin, HIV, and lactic acid.

Patient complained of worsening lethargy, fever, malaise, and back pain. Due to new onset transaminitis with question of possible sepsis superimposed on preeclampsia was suspected. Due to gestational age of 25 weeks 1 day of gestation with new suspected diagnosis maternal fetal medicine was consulted and patient required transfer to a facility with higher level of care neonatal intensive care unit. A course of celestone was initiated and antibiotics were changed to Zosyn. Maternal fetal medicine requested repeat blood cultures and urine cultures prior to transfer.

After transfer to higher level of care patient reported continued shortness of breath with mild abdominal pain. She continued to deny any obstetrical complaints except increased vaginal discharge. Vital signs remained notable for tachycardia to 110s and blood pressure 90s/50s with oxygen saturation greater than 95% on 6 liters of nasal cannula.

Sterile Speculum exam was performed and no genital lesions were visualized however thin, serous fluid was noted in vaginal vault. Of note, patient denied a history of HSV-1 or 2 or any symptoms consistent with HSV lesions. Laboratory review of transfer labs was notable for WBC of 8K with left shift, platelets of 136 and AST of 155 and ALT of 101. Creatinine was normal. Chest radiograph was notable for perihilar consolidation as well as left pleural effusion.

Pulmonology was consulted for assistance with acute respiratory failure. Pneumonia and pulmonary edema were suspected causative agents of respiratory failure secondary to aggressive fluid hydration. As she was stable on 6 L nasal cannula, intravenous fluid hydration was limited to allow for auto-diuresis.

Due to patient's blood pressures stabilizing a hypertensive disorder of pregnancy was not highly suspected by maternal fetal medicine. The patient's fever, rising LFTs and thrombocytopenia were thought to possibly be secondary to viral etiology as all other cultures remained negative. TORCH titers, EBV serology and HSV PCR of the vaginal fluid were obtained. Zosyn was continued and Vancomycin as well as IV Acyclovir was initiated.

Over the next 72 hours, the patient's blood pressures and heart rate remained stable and she was gradually weaned to room air. Over the course of the next two days of hospitalization the patient remained afebrile, WBC remained within normal limits, platelets improved to 180K and transaminitis ultimately began to normalize.

The HSV-I/II IgM resulted returned as positive as well as the HSV-II PCR from vaginal fluid. The rest of the TORCH titers were within normal limits. Antibiotics were discontinued and she was transitioned to PO Acyclovir 800 mg five times per day for ten days. For the remainder of pregnancy was then instructed to take 400 mg three times per day for suppression.

Extensive counseling was performed in regards to the potential for fetal HSV infection however it was discussed that the only way to confirm whether or not there was transplacental passage would be to perform an amniocentesis, but that this would carry the potential risk of introducing the virus into the amniotic fluid if it was not currently present. Counseling was also provided for the need for ongoing ultrasound surveillance as well as the importance of delivering at a hospital with NICU support for neonatal evaluation. She was ultimately discharged home on HD#6 with plans to follow up with primary OB.

Patient had follow-up with family medicine provider for obstetrical care at an outlying facility. A maternal fetal medicine specialist at another outlying facility also followed the pregnancy as well. Serial fetal growth ultrasounds performed were reassuring for appropriate fetal growth. The patient was continued on the recommended acyclovir dosing for the remainder of the gestation. Liver enzymes were followed as well for the remainder of the gestation and were found to remain within normal limits. The patient was admitted at 36 weeks 1 day of gestation secondary to preterm premature rupture of membranes. The patient had no complaints of prodromal symptoms and did not receive a sterile speculum exam to evaluate for herpetic lesions at time of admission to labor and delivery as recommended by maternal fetal medicine. Liver enzymes and platelets were within normal limits at time of admission. Labor was augmented with pitocin and progressed to have a spontaneous vaginal delivery of viable neonate. The placenta was not sent to pathology for exam. Neonate was evaluated by pediatrician and had routine neonatal admission to hospital. The patient and neonate were discharged home on postpartum day 2. Patient had an uneventful postpartum course and was continued on acyclovir during the six-week postpartum period.

Discussion

A limited review of the literature was performed using PubMed, Up-to-date, and Medline databases. Key words used in the literature review search were: disseminated herpes simplex virus, disseminated HSV during pregnancy, herpes simplex complications during pregnancy, management of herpes simplex during pregnancy, sepsis during pregnancy, viral causes of sepsis during pregnancy, and rare infections complicating pregnancy. Multiple case reports were obtained as well as epidemiologic studies on herpes simplex.

Disseminated herpes simplex virus during pregnancy remains a rare complication of the infection. The greatest risk for disseminated disease is during the primary infection. The most serious complication of maternal genital herpes simplex virus infection is neonatal disease and dissemination of the disease in the mother [2]. There is an increased risk of disseminated herpes simplex virus during pregnancy secondary to the changes in the response of the immune system during pregnancy. HSV-2 infects nearly 50% of infants whose mothers have primary genital herpes at time of delivery.

The most common findings associated with HSV viremia are constitutional and central nervous system alterations as well as abdominal pain, dysuria, vaginal discharge, urinary retention, and skin lesions are less frequently reported. Disseminated HSV infection can be severe and life threatening with visceral involvement. The appropriate work-up for a febrile illness in pregnancy can be exhaustive [4]. The most common laboratory abnormality was elevated liver enzymes. Aseptic meningitis and sepsis of unknown origin were common forms of initial presentation of disseminated herpes as well. If continued re-evaluation and treatment remains unsuccessful after 48 hours a maternal fetal medicine and other appropriate specialist should be consulted.

Sepsis is one of the most common cause of maternal mortality in the 19th century [4]. In a review of documented cases of disseminated HSV during pregnancy, fever occurred in 96% of cases. The patients reported flu-like prodrome of fever, chills, malaise, myalgia, and anorexia. No lesions were present at the time of presentation in up to 50% of cases. Hepatitis occurred in greater than 50% of pregnant patients with the diagnosis. Due to these non-specific findings, common diagnosis of sepsis of unknown origin, and no mucocutaneous lesions upon the majority of patient presentations repeated complete physical exams including a pelvic exam should be performed [8].

Due to the complications of hepatitis, coagulopathy, neurological activity including seizures associated with disseminated herpes simplex, these findings can cause a misdiagnosis of complications of pregnancy such as HELLP syndrome, eclampsia, and acute fatty liver disease of pregnancy with an indicated preterm delivery of the neonate which can further increase the morbidity associated with the disease due to increase in neonatal intensive care unit admission as well as increased maternal morbidity due to not receiving appropriate anti-viral therapy.

The acquisition of genital herpes has been associated with intrauterine growth restriction, preterm labor, and congenital and neonatal herpes infections. The risk of neonatal infection varies from 30% to 50% for HSV infections with onset in the last trimester of pregnancy. Risk to the fetus and neonate are well known by physicians, what is not well known is the risk to maternal health from a primary herpes infection if it were to become disseminated. A greater than 50% maternal mortality rates for disseminated herpes simplex are reported when unrecognized and therapy not initiated in a timely manner [3]. With several conditions associated with hepatic abnormalities during the latter part of gestation, clinicians must keep disseminated herpes simplex virus on the differential diagnosis since a large amount of the population are at risk of contracting herpes during pregnancy.

With the incidence of herpes simplex virus infection increasing throughout the population and risk of dissemination increased during pregnancy this raises multiple questions for screening: Should women at risk for a primary herpes simplex infection during pregnancy be screened routinely throughout pregnancy? With a known history of herpes simplex virus with genital lesions should women undergo sterile speculum exams during the latter third of pregnancy with document negative findings until onset

of active labor or at time of induction? Should there be an admission protocol during initial evaluation during active labor?

Currently the American College of Obstetricians and Gynecologist does not recommend routine HSV screening during pregnancy. Serological evaluation is only indicated with a personal history of herpes simplex virus or with new onset signs and symptoms of a primary outbreak during pregnancy. Under current guidelines suppressive therapy is recommended starting at 36 weeks of gestation. Vaginal delivery is appropriate route of delivery in the absence of genital herpetic lesions or prodromal symptoms. [6] Cesarean section is only indicated in women with active genital lesions or prodromal symptoms. Even though the incidence of neonatal disease is low when there is recurrent maternal disease a cesarean section is still recommended due to potentially serious neonatal disease [8]. Further investigation into the true incidence of primary herpes simplex during pregnancy, complications from disseminated disease during pregnancy, and the maternal and neonatal outcomes from disseminated disease will need to be performed to evaluate if changes in the guidelines for screening throughout pregnancy for those at increased risk of disease should be routinely screened.

References

1. Anzivino E, Fioriti D, Mischitelli M, Bellizzi A, Barucca V, Chiarini F, Pietropaolo V. *Herpes simplex virus infection in pregnancy and in neonate: status of art of epidemiology, diagnosis, therapy, and prevention*. *Virology Journal* 2009. 6-40.
2. Barefoot KH, Little GA, Ornvold KT. *Fetal Demise Due to Herpes Simplex Virus: An Illustrated Case Report*. *Journal of Perinatology* 2002. 22: 86-88.
3. Chatterjee A, Chartrand S, Harrison CJ, Felty-Duckworth A, Bewtra C. *Severe Intrauterine Herpes Simplex Disease with Placentitis in a Newborn of a Mother with Recurrent Genital Infection at Delivery*. *Journal of Perinatology*. 2001. 21:559-564.
4. Hussain NY. *Disseminated herpes simplex infection during pregnancy, rare but important to recognize*. *Qatar Medical Journal*. 2014. 11:61-64.
5. Linthavong OR, Franasiak J, Ivester T. *Febrile Illness in Pregnancy. Disseminated Herpes Simplex Virus*. *Obstetrics & Gynecology Green Journal*. 2013. 121: 675-681.
6. Scott LL, Hollier LM, McIntire D, Sanchez PJ, Jackson GL, Wendel GD. *Acyclovir suppression to prevent recurrent genital herpes at delivery*. *Infectious Disease Obstetrics Gynecology*. 2002. 10:71-77.
7. Young EJ, Chafizadeh E, Oliveira VL, Genta RM. *Disseminated Herpes virus Infection During Pregnancy*. *Clinical Infectious Disease*. 1996. 22:51-58.
8. Hollier L, ACOG Committee on Practice Bulletins. *ACOG Practice Bulletin: Management of Herpes in Pregnancy*. *Clinical Management Guidelines for Obstetricians-Gynecologist*. 2007. 82.