Hantavirus Pulmonary Syndrome in Pregnancy

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This comprehensive case review of hantavirus pulmonary syndrome (HPS) during pregnancy in 5 women characterizes the effect of Sin Nombre virus infection on maternal and fetal outcomes. Histopathologic, serological, and clinical information were evaluated for evidence of vertical transmission. Maternal ages ranged from 20 to 34 years and gestational ages from 13 to 29 weeks. Symptoms, physical findings, and laboratory values other than those related to pregnancy were not noticeably different from those of nonpregnant patients with HPS, although fevers were somewhat lower. One maternal death and 2 fetal losses occurred. Gross, microscopic, and immunohistochemical examination for hantavirus antigen were done on 2 fetal autopsies and 3 placentas showing no evidence of transplacental hantavirus transmission. There was no serological evidence of conversion in the 3 surviving children. Maternal and fetal outcomes of HPS appear similar to those of nonpregnant HPS patients and of pregnant patients with other causes of acute respiratory distress syndrome. No evidence of vertical transmission of Sin Nombre virus was found.

Hantaviruses are lipid-enveloped, trisegmented, negative-sense RNA viruses that belong to the family Bunyaviridae. The genus name, Hantavirus, is derived from the Hantaan River in Korea, where the prototype virus Hantaan was first isolated from the striped field mouse (Apodemus agrarius) in 1976 [1]. Additional hantavirus species found primarily outside the Western Hemisphere include Seoul, Dobrava, and Puumala viruses; these viruses, together with Hantaan virus, are responsible for a spectrum of illness referred to as hemorrhagic fever with renal syndrome [2]. All hantaviruses are associated with a primary rodent reservoir, and their transmission to humans is thought to involve inhalation of aerosolized virus excreted in rodent urine and feces.

Hantavirus disease in the Western Hemisphere first emerged as a significant public health threat in the southwestern United States in 1993 [3, 4]. The newly recognized disease was named hantavirus pulmonary syndrome (HPS), and the etiologic agent was found to be a previously undescribed hantavirus, Sin Nombre virus (SNV) [5]. HPS is characterized by severe noncardiogenic pulmonary edema resulting in respiratory compromise often resembling acute respiratory distress syndrome (ARDS). The case-fatality rate of HPS is ~45% [3, 6].

As of October 1999, a total of 229 cases of HPS have been confirmed in the United States. Five of these patients were women who were pregnant at the time of their illness. Although much is currently known about ARDS during pregnancy from other causes [7–10], the effects of HPS on maternal and fetal outcomes has only brieﬂy been presented [11–14].

In addition, this case series of 5 pregnant women with HPS affords the unique opportunity to assess the possibility of vertical transmission of hantavirus from mother to child. Experience with other members of the family Bunyaviridae suggests that vertical transmission is a possibility [15–17].

Here we summarize the presentation, clinical course, and pregnancy outcome of 5 pregnant women with HPS and assess the available evidence regarding the possibility of vertical transmission of hantavirus from these women to their fetuses.

Methods

HPS is a reportable disease in most states in the United States. State health departments perform preliminary testing for antibodies to SNV and forward to the Centers for Disease Control and Prevention (CDC) a case-report form and specimens from persons who test positive. Suspected cases should meet the following CDC definition: a febrile illness (temperature >38.3°C) occurring in a previously healthy person characterized by bilateral, diffuse interstitial pulmonary edema that may radiographically resemble...
ARDS developing within 72 h of hospitalization, with respiratory compromise requiring supplemental oxygen; or an unexplained respiratory illness resulting in death with an autopsy examination demonstrating noncardiogenic pulmonary edema without an identifiable cause. Persons with an underlying medical condition such as malignancy or immunodeficiency or persons with an acute condition that provides a likely explanation for the respiratory distress, such as recent trauma, burn, or aspiration, are excluded from consideration. Case report forms provide demographic and limited epidemiological and clinical data for each suspected case patient; these data, along with the laboratory results noted below, are entered into the CDC's National HPS Surveillance Database. In addition to a compatible clinical illness, confirmed cases must have either serological evidence of hantavirus infection, positive results of reverse transcriptase-PCR (RT-PCR) testing for hantavirus RNA, or positive results of immunohistochemical testing for hantavirus antigen in tissues.

Pregnant case patients with HPS were ascertained by including all female patients found in the CDC's National HPS Surveillance Database who met the CDC definition for HPS and had had a positive pregnancy test at some point during their illness. A thorough abstraction of the medical record was done for each of the women meeting these criteria. When possible, fetal autopsy and placental tissue analyses were done at the hospitals involved and at the CDC. Standard gross examination was supplemented with formalin-fixed and paraffin-embedded microscopic sections, immunohistochemistry, and RT-PCR for SNV RNA. These techniques have been described in detail elsewhere [18, 19].

**Results**

As of October 1999, 5 (2.2%) of the 229 confirmed cases of HPS in the United States have occurred in pregnant women. Of these 5 patients, 2 were American Indian, 2 were non-Hispanic white, and 1 was Hispanic. They ranged in age from 20 to 34 years (table 1), were previously healthy, and were taking only prenatal vitamins at the time of their illness. No patient reported alcohol or substance use, and only patient 2 was a smoker. All patients had at least 1 prenatal visit and were not experiencing any complications of their pregnancy before being diagnosed with HPS. Gestational age at the time of diagnosis ranged from 13 to 29 weeks. None of the women had evidence of abnormal fetal development, distress, or complications of their pregnancies before presentation.

The frequencies of various presenting signs and symptoms for the 5 confirmed pregnant HPS patients were similar to those seen in nonpregnant patients (table 2) [6, 20, 21]. Notable differences in presentation include the lack of a documented fever for 3 of the 5 patients, although all gave a history of subjective fevers. Further differences are noted in the case descriptions below. Prodromal periods ranged from 1 to 5 days, and hospitalization of survivors ranged from 6 to 11 days. The 1 maternal fatality occurred within 24 h of admission, for a case-fatality rate of 20%. Two of the 5 pregnancies resulted in fetal death in utero. One infant was born prematurely with significant cerebral and pulmonary complications and died after discharge from the hospital. Clinical findings at the time of hospital admission and results of laboratory studies during their stay are summarized in table 2.

**Case Reports**

Patient 1 presented among the first HPS patients seen during the spring of 1993, before diagnostic reagents specific for SNV were developed. She was a 25-year-old American Indian, gravida 6 para 5, at 29 weeks of gestation. Her admitting diagnosis was viral pneumonia and ARDS. She came to the hospital to visit her husband, who was in the medical intensive care unit with the same diagnosis. Her husband was later confirmed to also have HPS. Chief complaints included fever, nausea, low back pain, cough, vomiting, and myalgias for 1 day prior to admission, and she experienced a syncopal episode in the emergency department. On examination, she had a tympanic temperature of 38.2°C and was noted to be tachypneic, tachycardic, and hypoxic. Rales were present on pulmonary auscultation, and diffuse pain was noted on abdominal palpation. Physical examination also

**Table 1.** Demographic characteristics of pregnant women with hantavirus pulmonary syndrome.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Onset</th>
<th>Initial diagnosis</th>
<th>Age (y)</th>
<th>Gravida, para</th>
<th>Gestation (w)</th>
<th>Race or ethnicity</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5/27/93</td>
<td>Viral pneumonia</td>
<td>25</td>
<td>6, 5</td>
<td>29</td>
<td>American Indian, non-Hispanic</td>
<td>Survived; Died; cerebral palsy, seronegative</td>
</tr>
<tr>
<td>2</td>
<td>10/20/93</td>
<td>Pneumonia</td>
<td>34</td>
<td>3, 2</td>
<td>13</td>
<td>White, non-Hispanic</td>
<td>Died; Fetal death in utero; negative immunohistochemistry</td>
</tr>
<tr>
<td>3</td>
<td>11/22/93</td>
<td>Pneumonia, possible urinary tract infection</td>
<td>20</td>
<td>2, 1</td>
<td>20</td>
<td>American Indian, non-Hispanic</td>
<td>Survived; Survived; healthy, seronegative</td>
</tr>
<tr>
<td>4</td>
<td>9/8/94</td>
<td>Viral syndrome, pyelonephritis</td>
<td>27</td>
<td>1, 0</td>
<td>17</td>
<td>White, Hispanic</td>
<td>Survived; Survived; healthy, seronegative, negative immunohistochemistry</td>
</tr>
<tr>
<td>5</td>
<td>1/31/98</td>
<td>ARDS, sepsis, abdominal pain</td>
<td>28</td>
<td>2, 1</td>
<td>16</td>
<td>White, non-Hispanic</td>
<td>Survived; Fetal death in utero; negative immunohistochemistry</td>
</tr>
</tbody>
</table>

**NOTE.** ARDS, acute respiratory distress syndrome. Dates are given as month/day/year.
revealed clear drainage from her nose and eyes. Her respiratory status rapidly deteriorated, and she was intubated and placed on mechanical ventilation. The following admission laboratory values were noted: WBC count, elevated with a left shift; hematocrit, 35%; and platelet count, 155,000 (table 2). Serum analysis showed mild metabolic acidosis, hyponatremia, and hypokalemia. Coagulation studies and liver function tests were within normal limits. Pulmonary artery occlusion pressures and inverse ratio mechanical ventilation were effective in maintaining adequate oxygen delivery. Despite these efforts, fetal heart tones were lost on the fourth hospital day, and a precipitous vaginal delivery of a male infant ensued.

Over the following days, this patient demonstrated a dramatic recovery. Her oxygen requirement decreased and she was weaned from the ventilator, she was extubated, and was able to breathe spontaneously and was extubated, was discharged from the hospital, and later died at home. No further information was available for this child, and an autopsy was not performed. Placental tissues were consistent with preterm spontaneous delivery and were not tested for viral antigens or nucleic acids. Results of serological studies for hantavirus at the child’s birth were negative.

Patient 2 was a 34-year-old white woman, gravida 3 para 2, at 13 weeks of gestation with no significant past medical history aside from light tobacco use. She was seen in a community hospital emergency department complaining of shortness of breath and nonproductive cough with a 5-day history of fever, chills, headache, myalgias, weakness, and anorexia. She also noted watery eyes, a runny nose, and a sore throat. At this time, the patient was found to be afebrile, hypoxic, tachycardic, and hypotensive. She had a syncopal episode in the emergency department and was admitted to the hospital. Physical examination showed “congested nasal mucosa with a red throat and tympanic membranes and coryza,” bilateral rales and rhonchi, tachycardia without murmur, and no rash. Her admission diagnoses included hypovolemia, dehydration, and bronchopulmonary pneumonia. The admitting physicians were concerned that she was developing the HELLP (hemolytic anemia, elevated liver enzymes, and low platelets) syndrome. She was admitted to the medical intensive care unit. Admission laboratory values showed a slight elevation of her WBC count with a left shift, hemoconcentration, and significant thrombocytopenia (table 2). Mild coagulopathy and slightly elevated liver transaminase levels were also noted. Her serum bicarbonate level dropped to 11 meq/L and her arterial pH fell to 7.12 as her respiratory status worsened.

Table 2. Clinical and laboratory findings on admission and during hospitalization for 5 pregnant women with hantavirus pulmonary syndrome.

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (°C)</td>
<td>38.2 (36.9-39.5)</td>
<td>37.7 (37.7)</td>
<td>36.8 (36.8-37.2)</td>
<td>36.8 (36.8-37.2)</td>
<td>35.9 (35.9-37.2)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>104 (72-123)</td>
<td>136 (93-188)</td>
<td>135 (114-153)</td>
<td>76 (72-160)</td>
<td>170 (95-150)</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>20 (16-39)</td>
<td>20 (20-33)</td>
<td>30 (20-32)</td>
<td>16 (16-32)</td>
<td>44 (20-44)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>123 (86-132)</td>
<td>90 (34-118)</td>
<td>98 (98-134)</td>
<td>98 (80-118)</td>
<td>100 (75-130)</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>94 (79-99)</td>
<td>94 (76-98)</td>
<td>86 (84-97)</td>
<td>82 (82-97)</td>
<td>79 (79-97)</td>
</tr>
<tr>
<td>Chest radiograph*</td>
<td>Bilateral interstitial infiltrates</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Alveolar infiltrates</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Effusions</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Fetal heart tones (bpm)</td>
<td>140 (125-166)</td>
<td>160 (135-170)</td>
<td>145 (128-155)</td>
<td>150 (145-160)</td>
<td>0</td>
</tr>
<tr>
<td>Ultrasound findings</td>
<td>Intrauterine, breech, weeks 28+</td>
<td>13.3 (9.3-22.7)</td>
<td>10.4 (10.4-12)</td>
<td>20.1 (13.2-20.1)</td>
<td>10.8 (10.8-11)</td>
</tr>
<tr>
<td></td>
<td>Intrauterine, 13 weeks</td>
<td>35.0 (25-38.1)</td>
<td>55.5 (49-66)</td>
<td>40.8 (32-40.8)</td>
<td>46.6 (36-48.4)</td>
</tr>
<tr>
<td></td>
<td>Intrauterine, 20 weeks</td>
<td>155 (103-291)</td>
<td>17 (13-19)</td>
<td>136 (85-136)</td>
<td>140 (140-151)</td>
</tr>
<tr>
<td></td>
<td>Band forms (%)</td>
<td>8 (0-8)</td>
<td>15 (15-21)</td>
<td>34 (0-34)</td>
<td>44 (6-44)</td>
</tr>
<tr>
<td></td>
<td>Albumin (g/dL)</td>
<td>3.0 (1.7-3)</td>
<td>2.7 (2.5-2.7)</td>
<td>ND (2.2-4.2)</td>
<td>2.7 (2.3-2.7)</td>
</tr>
<tr>
<td></td>
<td>Partial thromboplastin time (s)</td>
<td>40 (24-26)</td>
<td>77 (56-77)</td>
<td>ND</td>
<td>41 (28-41)</td>
</tr>
<tr>
<td></td>
<td>Fibrinogen (mg/dL)</td>
<td>510 (427-636)</td>
<td>266 (266)</td>
<td>ND</td>
<td>260 (260-354)</td>
</tr>
<tr>
<td></td>
<td>Arterial blood pH</td>
<td>7.49 (7.38-7.58)</td>
<td>7.45 (7.12-7.45)</td>
<td>7.43 (7.43-7.47)</td>
<td>7.42 (7.42-7.46)</td>
</tr>
<tr>
<td></td>
<td>CO2 (mm Hg)</td>
<td>28 (25-46)</td>
<td>24 (21-52)</td>
<td>27 (27-30)</td>
<td>19.9 (19.9-21)</td>
</tr>
<tr>
<td></td>
<td>PO2 (mm Hg)</td>
<td>44 (30-132)</td>
<td>45 (36-139)</td>
<td>52 (52-85)</td>
<td>90.1 (59-90.1)</td>
</tr>
</tbody>
</table>

NOTE: Data are value on admission (range during hospitalization). ND, not determined.

* Findings on initial radiograph: Y, yes; N, no.
Her condition rapidly deteriorated, necessitating intubation and pulmonary artery catheterization. Despite maximum pharmacological and inotropic support and successful cardioversion for ventricular tachycardia and fibrillation, she died within 20 h from the time of admission. The diagnosis of HPS was made at autopsy. Lung and kidney tissues from this patient were both positive for SNV by immunohistochemistry. Fetal tissues (lung, kidney, heart, liver, adrenals, intestine, and spleen) were negative for SNV by immunohistochemistry at the CDC laboratory.

Patient 3 was a 20-year-old American Indian woman, gravida 2 para 1, who contracted a mild case of HPS in November 1993 during the 20th week of pregnancy. Her chief complaints included a productive cough, fever, sweats, and back pain. She noted several days of diffuse abdominal pain, diarrhea, and urinary frequency with burning on urination. Her initial diagnosis was pneumonia and a possible urinary tract infection. Because of an increasing oxygen requirement, she was transferred to an intensive care unit and was hospitalized for 8 days in moderate respiratory distress. She was never intubated. The diagnosis of HPS was confirmed by serology on the fourth hospital day. This patient went on to have an uncomplicated vaginal delivery of a healthy, 7-pound 9-ounce, full-term girl. There was nothing abnormal noted on gross examination of the placenta, and it was not tested further. The child tested negative for IgG antibody to SNV at 12 months of age and appears to be healthy.

Patient 4, a 27-year-old Hispanic woman, presented in September 1994 in the 17th week of her first pregnancy. Her chief complaints included 2 days of dry cough, low back pain, vomiting, fever, and chills, as well as burning on urination. Physical examination revealed an ill-appearing gravid female with mild bilateral periorbital “puffiness,” decreased breath sounds, and tachycardia. She was admitted with a diagnosis of pyelonephritis in pregnancy and a “viral syndrome.” Because of rapidly worsening respiratory compromise, she was transferred to an intensive care unit where the diagnosis of HPS was confirmed serologically. Her respiratory status stabilized under treatment with high-flow oxygen, and she did not require intubation. She was discharged after 5 days and went on to have an uncomplicated spontaneous vaginal delivery of a healthy, 7-pound, full-term boy.

Placental tissue was tested and had no evidence of SNV infection by gross, microscopic, and immunohistochemical analyses. Cord blood and serial serum samples from the child were negative for IgM antibody to SNV and demonstrated expected loss of titratable maternal IgG antibody to SNV. This child appears to be healthy with no obvious sequelae of the maternal infection.

Patient 5 was a 28-year-old white woman at 16 weeks of gestation who presented in January 1998 complaining of fever, chills, headache, sore throat, cough, dyspnea, epigastric pain, and vomiting. She visited her primary doctor on the fourth day of her illness and was diagnosed with probable influenza. She was given recommendations for symptomatic relief and referred to her obstetrician that same day, who determined that her pregnancy appeared normal. The following day she presented to the emergency department in respiratory distress and was intubated and transferred to a tertiary care facility with the diagnosis of ARDS, sepsis, and abdominal pain. On admission, her WBC count was 43,100 (with 36% band forms and 12% atypical lymphocytes), her platelet count was reduced to 47,000, and the hematocrit was 51% (table 2). Elevated liver enzymes and a low albumin level were also noted. Abdominal ultrasound showed a thickened gallbladder wall but no stones or evidence of biliary obstruction.

On transfer, the patient was noted to have a small amount of vaginal bleeding and a closed cervix on examination. Fetal heart tones were not found. Pelvic ultrasound done on the second hospital day noted no fetal cardiac motion. That evening, the patient delivered a nonviable 93-g male fetus, and the placenta was delivered later by curettage. Culture of amniotic fluid was negative. Fetal tissues (lung, kidney, heart, liver) and placenta were negative for SNV by immunohistochemistry analyses at the CDC laboratory.

The patient experienced a moderate improvement in her cardiovascular and pulmonary status after her delivery. She remained intubated for a total of 9 days and did not have an oxygen requirement when discharged from the hospital 2 days after extubation.

Discussion

The presentation of a pregnant woman with noncardiogenic pulmonary edema is a rare and serious scenario with a broad differential diagnosis that now includes HPS. These 5 cases represent our only experience with HPS in pregnancy. Changes in maternal physiology and the range of pregnancy-related complications that can cause or result in ARDS make generalizations regarding the effects of HPS difficult in this small subgroup of patients.

ARDS in pregnancy has only recently been examined [7–9]. Mortality due to ARDS during pregnancy is not significantly different from that of nonpregnant patients (43%–44%) and is associated with marked perinatal morbidity and a high degree of fetal loss (23%) [9, 22, 23]. Infectious diseases remain the most prominent among known etiologic factors resulting in ARDS during pregnancy, although pregnancy-related conditions, including preeclampsia, eclampsia, and hemorrhage, also play a significant role. In 1 case series examining 16 pregnant women with ARDS, Mabie et al. [7] noted infectious diseases as the primary etiology in half of the cases, 4 of which were due to viral pneumonias. One patient with influenza A survived but had a spontaneous delivery at 22 weeks. Two of 3 patients with pneumonia due to varicella-zoster virus survived and had normal uncomplicated deliveries. The third patient died after
spontaneous delivery of a 30-week infant. This child survived but had a complicated course, including prolonged mechanical ventilation due to respiratory distress syndrome, intraventricular hemorrhage, and patent ductus arteriosus, not unlike case 1 described above.

It is unclear what the physiological changes of pregnancy may have contributed to the clinical outcomes of these 5 women with HPS. Although the small numbers limit useful comparison with nonpregnant patients with HPS, it is clear that changes related to pregnancy can alter parameters believed to be important in screening for patients with HPS and in managing patients with ARDS. Physiological anemia due to expanded intravascular volume can adversely affect oxygen delivery and may mask the usual hemoconcentration seen in HPS. Only 2 of the 5 patients in this study developed hematocrit values of 50% [21]. The increase in intra-abdominal volume with pregnancy effectively reduces pulmonary compliance, thus decreasing functional residual capacity and possibly complicating positive pressure ventilation. Furthermore, there may be competition because blood is shunted to vascular beds in the placenta, thus increasing overall oxygen demand.

These factors may contribute to the supposed benefit gained from delivery for the pregnant patient with ARDS [7, 10, 22, 24]. Presently, there is no clear evidence to support therapeutic or induced delivery for pregnant patients with ARDS due to hantavirus infection. Clearly, gestational age must be considered, as it limits viability of the fetus. Most authors suggest individualized care with attempts at vaginal delivery if necessary, reserving cesarean section for standard obstetrical indications [11, 22].

The physiological and anatomic changes of pregnancy may explain the unexpected signs and symptoms seen in this case series. For example, urinary complaints and sinusitis are two of the most common reasons for women to seek medical attention during pregnancy. This may be why two patients in this series presented with primarily urinary tract complaints. Watery eye drainage and sinusitis were not seen in the initial clinical characterization of HPS but may represent what is an otherwise common complaint in pregnant females. Two of the 5 patients also complained of sore throats, which has been previously suggested to be a negative predictor for HPS [21]. The significance of these findings is unclear.

Particularly noteworthy within this group of patients was the differential diagnosis considered for the 1 patient who died of HPS. She was thought to have the variant of preeclampsia known as HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome. The common pathogenesis leading to multiple organ system failure that defines HELLP syndrome appears to be a vascular insult at the level of the capillary endothelium that has not yet been elucidated [25, 26]. Similarly, SNV infection appears to exert its effects at the level of the vascular endothelium leading to increased capillary leak, possibly making initial presentations of the two hard to differentiate. The notable difference between HELLP syndrome and HPS is that SNV hantavirus infection typically has its pathological effects on the organs of the chest (lung and heart) without causing significant liver, renal, or vascular injury elsewhere. Several studies have demonstrated marked accumulations of hantavirus antigens and genetic material primarily distributed within the pulmonary capillary endothelium [18, 19, 27]. Whether the insult is a direct result of viral infection or it occurs as a consequence of immune cell activity or the actions of mediators released from the systemic immunologic response is not clear, and further study is warranted.

The list of viruses known to be transmitted via the placenta is long and includes several with well-known detrimental effects on the growth and development of the fetus [28, 29]. Rubella, the classic example, causes only a mild illness in the mother yet leads to growth retardation, malformations, and sometimes death of the fetus. On the other hand, cytomegalovirus infection may go completely unnoticed in the fetus after the mother experiences a mild or subclinical primary infection in pregnancy. Some viruses (e.g., influenza virus) are known to never be transmitted vertically to the fetus, and still others may variably cause fetal infections (hepatitis B virus, HIV, lymphocytic choriomeningitis virus) [28, 29]. Although there is no laboratory or field evidence of vertical hantavirus transmission within rodent reservoir species [30–34], another group of rodent-borne viruses, the arenaviruses, do show evidence of vertical transmission. In rodents, these viruses regularly infect the fetus and result in chronic, viremic fetal infection that can be largely nonpathogenic (lymphocytic choriomeningitis virus and Lassa virus) or severely affect the pups (Machupo and Junin viruses). In humans, arenaviruses can also infect the placenta and fetus and can result in fetal damage and abortion [4]. Thus, the lack of evidence for vertical transmission of hantaviruses in humans or rodents is an important contrast from the vertical transmission observed for arenaviruses.

Transplacental (in utero) infection generally implies that the virus is capable of infecting placental trophoblast tissue and passing directly to the fetal circulation. Indirect modes of transmission in the absence of obvious placental infection have been proposed and could occur in HPS. It is possible that small, virally induced vascular lesions may allow diapedesis of infected maternal leukocytes or coated RBCs into the fetal circulation, as has been proposed in diseases due to other viruses such as HIV [29]. The placental samples submitted for pathological examination in this study demonstrated no gross or microscopic evidence of infection. All available tissue samples were negative by immunohistochemistry. Likewise, placental and fetal tissue from the 2 cases with fetal death (patients 2 and 5) revealed no evidence of hantavirus infection. These data argue against vertical transmission by a transplacental route.

The 2 women with milder cases of HPS (patients 3 and 4) in this study went on to have uncomplicated full-term vaginal deliveries without any further evidence of hantavirus infection.
Although acutely infected, patient 1 delivered a 29-week infant with multiple perinatal complications most likely due to prematurity and/or maternal hypoxemia and hypotension. So far, these children have had no serological evidence of infection. This provides evidence against vertical transmission by a perinatal route in the acutely infected or convalescent HPS patient.

It should also be noted that the definition of vertical transmission can include perinatal transmission in breast milk. Examples of this exist for other viruses (mumps, HIV, and cytomegalovirus) [28, 29]. Presently there is no conclusive evidence of this type of transmission in any reported human cases or animal models involving the hantaviruses causing HPS. Our case series suggests that neither transplacental nor perinatal transmission occur in HPS in North America.

Review of human cases of hantavirus infection during pregnancy found only 14 reports in the literature [11–17, 35–41]. Four of these citations suggest maternal-to-fetal transplacental transmission of hantavirus. Three were in pregnant women with hemorrhagic fever with renal syndrome due to Hantaan virus [15–17], but only 1 of these was clearly documented by serological testing of the fetus [15]. The first of these cases reporting transmission occurred in a Korean woman acutely infected with Hantaan virus (documented by “a serological test”) [16]. She had a spontaneous abortion following a maternal hypotensive episode at ~7 months of gestation. The fetal autopsy demonstrated systemic hemorrhage throughout the lungs, kidney, and adrenal glands that was thought consistent with Korean hemorrhagic fever. There was no mention of serological testing of the fetus and no conclusive evidence of transplacental infection. The authors did note that the fetal death could have resulted from hypotension or other complications of maternal systemic infection. In fact, such findings on fetal autopsy are consistent with those seen in pregnant women suffering from other illnesses causing profound hypotension [9, 23].

The most convincing case in the literature was reported by Lee [15] in 1989. He describes a 28-year-old Korean woman in her eighth month of gestation who developed hemorrhagic fever with renal syndrome due to a documented primary Hantaan virus infection. On the 28th day of her hospitalization, well after her acute renal insult had begun to resolve, she spontaneously delivered a 3.3-kg fetus who survived only 11 h. Later, serological testing demonstrated IgM at a titer of 1 : 256 in fetal cord blood. The fetal autopsy demonstrated hemorrhagic lung, kidney, and adrenal tissue similar to that noted in the earlier cases.

It is interesting to note that several human case reports of Hantaan virus [39, 40], Puumala virus [36–38, 41], and SNV [11, 12] infections have found no evidence of vertical transmission in the pregnant women they studied. The fact that vertical transmission occurs inconsistently in Hantaan virus infection and does not appear to occur with closely related viruses such as Puumala virus and SNV suggests that this is a heterogeneous group of viruses with low and variable rates of transplacental transmission.

These 5 patients represent the only women known to be infected with SNV during pregnancy. These cases demonstrate epidemiological features and mortality similar to those observed for nonpregnant patients with HPS. There is currently no evidence from these cases to support vertical transmission of SNV to the fetus in utero or perinatally.

The differential diagnosis of ARDS in pregnancy, although a rare complication, continues to grow in complexity, and HPS should be considered in patients from areas of endemicity who have a history of possible exposure. It should be reiterated that the physiology and immunology of pregnancy may lead to variations in the typical presentation and course of infection of HPS. There remains no conclusive evidence to support early, induced delivery in HPS patients or other pregnant patients with ARDS. Clinical management should be individualized, with decisions regarding maternal-fetal management made jointly between critical care and obstetrical specialists.

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References


