A 31-year-old, otherwise healthy, woman, (gravida 0 and para 0), at 15 weeks of gestation was admitted to our hospital on October 29, 2004 due to fever, chills, eyeball pain and back pain of 4 days' duration. The patient had undergone intrauterine insemination on June 24, 2004 before achieving pregnancy. She began to complain of facial edema and blurred vision just after admission. She denied having a cough, diarrhea or dysuria. She and her husband were beef cattle-breeders in the rural Yangju area of Gyeonggi Province, Korea. On examination, her blood pressure was 110/80 mm Hg and her temperature was 38.3°C. She displayed flushing of the face, conjunctival hemorrhage and bulbar conjunctival edema. Her chest auscultation was normal. Mild tenderness was bilaterally found on her costovertebral angle, but no skin rash was evident. The laboratory tests revealed the following: leukocyte count: 21,300/μL (normal range: 4,000-10,000/μL), platelets: 83,000/μL (normal range: 150,000-400,000/μL), creatinine: 0.9 mg/dL (normal range: 0.7-1.4 mg/dL), aspartate transaminase: 67 U/L (normal range: <40 U/L), sodium: 135 mmo/L (normal range: 135-145 mmo/L), and potassium: 3.8 mmo/L (normal range: 3.5-5.5 mmo/L). Urinalysis revealed proteinuria and hematuria. Cultures of her blood and urine were sterile. Fetal ultrasound showed normal fetal growth that was consistent with the gestation dates.
| Presentation | Age (year) | Gestation (week) | Possible risk of exposure | Serodiagnosis in mother | Hospital course and maternal outcome | Delivery and fetal outcome | Reference |
|--------------|-----------|------------------|--------------------------|-------------------------|-------------------------------------|----------------------------|-----------|
| Nov 1978     | 27        | 28               | Unknown                  | IF positive but titer unknown | Recovered after hemodialysis | Stillbirth of 1,050 g  
Autopsy: systemic hemorrhage, suspicious transplacental infection | 11 |
| Nov 1985     | 26        | 18               | Unknown                  | IF positive but titer unknown | Recovered without sequelae | CS due to previous CS at 40 weeks' gestation  
Healthy infant of 3,400 g | 12 |
| Nov 1985     | 25        | 19               | Unknown                  | IF positive but titer unknown | Recovered without sequelae | VD at 38 weeks' gestation  
Healthy infant of 2,580 g | 12 |
| ? 1989(?)    | 28        | 29               | Unknown                  | IF 1:4,096               | Uterine bleeding, recovered without sequelae | VD  
Infant of 3,300 g died 11 hours after birth  
IF 1:256 IgM in umbilical cord blood | 13 |
| Jan 1997     | 29        | 27               | Shopping in a farmer's market 1 month ago | IF 1:640 on HD 4, 1:5,120 on HD 12, 1:1,280 at delivery | Recovered without sequelae | CS due to previous CS at 39 weeks' gestation  
Healthy infant of 2,960 g  
IF 1:640 in umbilical cord blood at delivery | 14 |
| ? 1997      | 27        | 29               | Unknown                  | IF positive but titer unknown | Recovered without sequelae | VD at 39 weeks' gestation  
Healthy infant of 2,920 g | 15 |
| Nov 1998     | 29        | 30               | Visit to ancestral grave 1 month ago | IF positive but titer unknown | Recovered after emergency CS at HD 3 | MV due to IRDS  
1400 g at birth, 2,300 g at discharge (HD 40)  
IF negative | 16 |
| Nov 2004     | 27        | 15               | Breeding beef cattle     | HDPA 1:640 on HD 5, 1:2,560 on HD 14 | Recovered without sequelae | NFVD at 39 weeks' gestation  
Healthy infant of 2,900 g  
Present case | |

Abbreviation: IF, indirect immunofluorescence test; HDPA, high-density particle agglutination test; CS, cesarean section; VD, vaginal delivery; IRDS, infant respiratory distress syndrome; MV, mechanical ventilation; HD, hospital day

Her condition deteriorated over the following days. Her blood pressure dropped to as low as 60/40 mmHg despite massive administration of physiologic saline on day 2, and her platelet count decreased to 15,000/μL on day 5. Her oliguria and elevated serum creatinine levels of up to 4.2 mg/dL necessitated the administration of diuretics intermittently from day 3 to day 7. However, from day 8 her renal functions progressively improved. The patient recovered completely and was discharged on day 14. The antibody titer for Hantaan virus, which was determined using a high-density particle agglutination test (Hantadia, Greencross, Korea) was 1:640 on day 5. A repeat titer showed an increase to 1:2,560 at the time of discharge, but it was 1:1,280 two weeks after discharge. Serologic tests for Leptospira, Orientia tsutsugamushi and HIV were negative.

The pregnancy continued uneventfully, and the patient was lost to follow-up. Six months later, she vaginally delivered a 2,900-g healthy female infant without complications at another hospital. However, no additional tests for Hantaan virus were performed on her or her baby at the time of delivery.

**DISCUSSION**

Hantavirus infection that complicates pregnancy has rarely been reported in the literature, although hantavirus infections in some women can lead to obstetric and fetal complications. In Korea, only 8 cases of HFRS complicating pregnancy (including the present case) have been reported. These are summarized in Table 1. The gestational age at the time of diagnosis ranged from 15 to 29 weeks, and none of the reported patients showed evidence of abnormal fetal development, distress or pregnancy complication before presentation. Of these 8 cases, the pregnancies did not achieve full-term in three of the pregnant women, and it’s interesting that they were all in the early third trimester of pregnancy when they contracted the disease. These three pregnancies resulted in intrauterine fetal death, preterm delivery but fetal death after birth, and...
preterm cesarean section, respectively\textsuperscript{11, 13, 16). Among these cases, only one case of transplacental transmission of Hantaan virus was confirmed both serologically and pathologically\textsuperscript{13}). In another case, the stillborn infant showed strong pathological evidence of Hantaan virus infection\textsuperscript{11). However, it could be argued that in this case any serologic testing of the fetus was not performed and the autopsy findings were consistent with those seen for pregnant women with other illnesses that cause profound hypotension\textsuperscript{17). In the other cases, including our case, the presence of transplacental Hantaan virus transmission remains unknown because the appropriate fetal laboratory tests were not performed.

The maternal and fetal outcomes of pregnancy complicated by HFRS have also been reported in China, where the most severe form of HFRS caused by Hantaan virus occurs (the same form occurs in Korea\textsuperscript{18-20). One of these China studies suggested there was maternal-to-fetal transmission, but the fetal infection was not unequivocally confirmed by any pathological and/or serological evidence\textsuperscript{20). Nevertheless, in a previous report, post-natal deformity was not observed in healthy babies born naturally to mothers who recovered from HFRS\textsuperscript{20). Infected cases by other hantaviruses such as Puumala virus\textsuperscript{3-6)} and Sin Nombre virus\textsuperscript{7-10) during pregnancy have also been noted. There have been no reported cases of HFS caused by Puumala virus that led to fetal death\textsuperscript{3-6). A case series of HPS in pregnancy showed that some Sin Nombre virus infections caused fetal complications, including fetal death in utero\textsuperscript{7). In contrast with Hantaan virus infections in pregnancy, there is no evidence of transplacental transmission to the fetus for Puumala virus or Sin Nombre virus\textsuperscript{3-7, 9, 10). For example, in a recent study of 5 pregnant women with HPS, one case of maternal death and 2 cases of fetal loss were identified, but no histopathological and/or serological evidence for the vertical transmission of Sin Nombre virus was found in any case\textsuperscript{7). These findings of hantavirus infection in pregnancy might suggest that Hantaan virus infection has a higher risk of transplacental transmission than other infections caused by other hantaviruses, but that this rate is still low. It might also be suggested that infections caused by Hantaan virus and Sin Nombre virus in pregnant women are more likely to cause severe fetal complications than does Puumala virus. However, these suggestions remain speculative because only a small number of cases of hantavirus infections in pregnant women have been reported in the literature to date.

In conclusion, hantavirus infection during pregnancy, especially that caused by Hantaan virus, can cause unfavorable obstetric and fetal outcomes. Although hantavirus infection occurs only rarely during pregnancy, this condition should be considered in the differential diagnosis involving fever, thrombocytopenia, hemorrhagic manifestations and acute renal failure in pregnancy, and especially when these symptoms are seen in an endemic area.

REFERENCES

1) Lee HW, Lee PIW, Johnson KM. Isolation of the etiologic agent of Korean Hemorrhagic fever. J Infect Dis 137:288-308, 1978
2) Peters CJ, Simpson GL, Levy H. Spectrum of hantavirus infection: hemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome. Annu Rev Med 50:331-545, 1999
3) Silberberg L, Rollin PE, Kerkouani G, Courdrier D. Haemorrhagic fever with renal syndrome and pregnancy: a case report. Trans R Soc Trop Med Hyg 87:65, 1993
4) Partanen S, Kahanpaa K, Peltola J, Lahdevirta J. Infection with the Puumala virus in pregnancy: case report. Br J Obstet Gynaecol 97:274-275, 1990
5) Partanen S, Sarioja A, Lahdevirta J. Lack of evidence of Puumala virus infection in patients with spontaneous abortion. Eur J Clin Microbiol Infect Dis 12:142-143, 1993
6) Prebensen D. Nephropathia Epidemica infection during first trimester of pregnancy: normal fetal outcome. Acta Obstet Gynecol Scand 76:884-885, 1997
7) Howard MJ, Doyle TJ, Koster FT, Zaki SR, Khan AS, Petersen EA, Peters CJ, Bryan RT. Hantavirus pulmonary syndrome in pregnancy: clinicopathological characteristics. J Clin Virol 20:128-133, 1998
8) Chun SH, Chang MY, Kim YJ, Woo BH. Two cases of Korean Hemorrhagic Fever complicated with pregnancy. Korean J Obstet Gynecol 35:778-782, 1992
9) Gilson GJ, Macullua JA, Nevils BG, Izquierdo LE, Chatterjee MS, Curet LB. Hantavirus pulmonary syndrome complicating pregnancy. Am J Obstet Gynecol 171:550-554, 1994
10) Kim CH, Ra MJ, Moon YJ, Hwang JH, Kim SR, Hwang YY. A case of pregnancy complicated with Korean Hemorrhagic Fever (in Korean). Korean J Obstet Gynecol 10:36-40, 1997
11) Chun SH, Chang MY, Kim YJ, Woo BH. Two cases of Korean Hemorrhagic Fever complicated with pregnancy (in Korean). Korean J Obstet Gynecol 35:778-782, 1992
12) Lee HW, Hemorrhagic fever with renal syndrome in Korea. Rev Infect Dis 11(Suppl 1):S864-S876, 1989
13) Kim CH, Ra MJ, Moon YJ, Hwang JH, Kim SR, Hwang YY. A case of pregnancy complicated with Korean Hemorrhagic Fever (in Korean). Korean J Obstet Gynecol 40:2892-2897, 1997
14) Pak SM, Kim SS, Kim HY, Son YS. A case of Korean Hemorrhagic Fever complicated with pregnancy (in Korean). J Korean J Obstet Gynecol 41:1220-1224, 1998
15) Choi E, Kim MR, Ro DY, Choi OC, Namkoong SE. A case of hantavirus pulmonary syndrome complicating pregnancy (in Korean). Korean J Obstet Gynecol 43:1282-1285, 2000
16) Ma RM, Xiao H, Jing XT, Lao TT. Hemorrhagic fever with renal
syndrome presenting with intrauterine fetal death: a case report. J Reprod Med 48:661–664, 2003

19) Liu YF, Yan PS, Wang BY, Liu J, Wang NP, Zhu XS, Huang M, Chen BQ. Intrauterine infection of epidemic hemorrhagic fever (EHF) via placenta. Chin Med J 100:756–758, 1987

20) Peng H, Tang S, Qi X. Clinical study on intrauterine hemorrhagic fever with renal syndrome virus infection (in Chinese). Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi 16:281–282, 2002