ORIGINAL ARTICLE VIROLOGY

Pregnancy and Crimean-Congo haemorrhagic fever

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Abstract

Crimean-Congo Hemorrhagic fever (CCHF) is a potentially fatal viral infection with reported case fatality rates of 5–30%. Humans become infected through tick bites, by contact with a patient with CCHF during the acute phase of infection, or by contact with blood or tissues from viraemic livestock. In this first report in the literature, we present the characteristics of three pregnant women with CCHF infection and the outcome of their babies. Transmission of the CCHF infection could be either intrauterine or perinatal. In endemic regions, CCHF infection should be considered in the differential diagnosis of HELLP syndrome (haemolytic anaemia, elevated liver enzymes, low platelet count), and obstetricians should be familiar with the characteristics of CCHF infection. In the aetiology of necrotising enterocolitis, CCHF should be considered.

Keywords: Crimean-Congo haemorrhagic fever, pregnancy
Original Submission: 22 August 2008; **Revised Submission:** 9 March 2009; **Accepted:** 10 March 2009
Editor: E. Gould
Article published online: 23 September 2009
Clin Microbiol Infect 2010; **16:** 647–650
10.1111/j.1469-0691.2009.02905.x

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Introduction

Crimean-Congo haemorrhagic fever (CCHF) is a fatal viral infection. The virus belongs to the genus *Nairovirus* in the family *Bunyaviridae*, and causes severe disease in humans, with reported case fatality rates of 5–30% [1]. A CCHF outbreak in Turkey was first reported in 2003 [1–3]. By the year 2008, more than 3200 CCHF-confirmed patients had been recorded at the Ministry of Health of Turkey. The main group of vectors involved in CCHF virus transmission appears to be ticks of the genus *Hyalomma*. Humans become infected through the bites of ticks, by contact with a patient with CCHF during the acute phase of infection, or by contact with blood or tissues from viraemic livestock [1]. However, infection during pregnancy has not been described yet. In this first report in the literature, we present the characteristics of three pregnant women with CCHF virus infection and the outcome of their babies.

Materials and Methods

All of the pregnant CCHF patients who had been hospitalized between 2003 and 2008 in the Infectious Diseases and Clinical Microbiology Clinic of Ankara Numune Education and Research Hospital were included. The acute and convalescent sera of all patients were sent to the Refik Saydam Hygiene Centre of Turkey. The serological studies were performed using ELISA, and PCR was performed for all of the acute cases. The biochemical laboratory parameters were measured on a daily basis after admission of the patient to the hospital. Serological and PCR results were obtained with a delay of several weeks after the samples were sent to the laboratory.

Results

The mean age of the three pregnant women involved in the study was 33 years. Two of three cases had a history of tick bite.

TABLE 1. Characteristics of the patients and their babies

	First case	Second case	Third case
Age (years)	40	20	38
History of tick bite	+	–	+
Symptoms on admission			
Temperature (°C)	37.8	37.5	38.7
Bleeding	Vaginal, epistaxis	Subconjunctival, ecchymosis at the antecubital fossa	Haematemesis, epistaxis
Laboratory findings on admission			
White blood cells (/mm^3)	6700	3400	1200
Platelets (/mm^3)	8000	53 000	12 000
Aspartate aminotransferase (IU/L)	591	813	814
Alanine aminotransferase (IU/L)	163	539	116
Lactate deyhdrogenase (IU/L)	1079	741	2162
Creatinine phosphokinase (IU/L)	2132	64	1403
Prothrombin time (sec)	15.4	12.4	13.4
Activated partial thromboplastin time (sec)	42.4	27.6	104.7
International normalized ratio	1.22	1.10	1.07

First case

On 28 May 2005, a previously healthy pregnant woman at an estimated 38th week of gestation was admitted to the Obstetrics and Gynaecology Clinic of Ankara Numune Education and Research Hospital. She was prediagnosed with haemolytic anaemia, elevated liver enzymes, and low platelet count (HELLP syndrome) (Table 1). On the day of admission, she underwent a caesarean section because of decreased fetal movement. On the second day of hospitalization, viral haemorrhagic fever was considered as the aetiology, and oral ribavirin was given. In serological studies, CCHF virus IgM and IgG were found to be positive by ELISA, and CCHF virus was not detected by PCR (Table 2). On the fifth day of hospitalization, she had a sudden abdominal pain. By ultrasound, fluid between the abdominal muscles and fluid in the anterior cul-de-sac were detected, and an intrauterine haematoma was noted (Fig. 1). She was re-operated on because of intramural haematoma, which was attributed to CCHF virus infection. During her stay in the hospital, she was given 22 units of fresh frozen plasma, and 54 units of thrombocyte solution. She was discharged, fully cured, after 20 days.

TABLE 2. The diagnoses of the cases

	Weeks of gestation at the time of CCHF virus infection	IgM	IgG	PCR	Outcome
First mother	38 weeks (term)	+	+	–	Survived
Baby	Caesarian section	–	+	+	Fatal
Second mother	19 weeks	+	NA	+	Survived
Baby	Vaginal delivery (term)	–	NA	–	Fatal
Third mother	28 weeks	+	–	+	Fatal
Fetus	Died with the mother	NA	NA	NA	Fatal

CCHF, Crimean-Congo haemorrhagic fever; NA, not applicable.

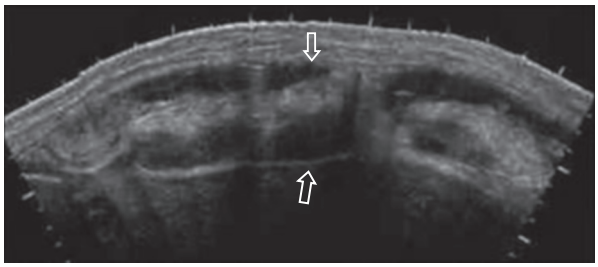

FIG. 1. Ultrasound image of the first case. Haematoma was developed after caesarean section.

The baby was delivered by caesarean section. At the first day of delivery, the clinical and laboratory findings for the baby were normal. The white blood cell (WBC) count was 4100/mm^3, the platelet (PLT) count was 248 000/mm^3, and the haemoglobin (Hb) level was 15.8 g/L. The baby was sent to Dr Sami Ulus Children's Hospital, Neonatalogy Clinic. On the fifth day, the WBC count was 8200/mm^3, the PLT count was 40 000/mm^3, and the Hb level was 11.1 g/L. The aspartate aminotransferase (AST) level was 5372 IU/L, the alanine aminotransferase (ALT) level was 962 IU/L, the creatinine phosphokinase level was 1808 IU/L, the total bilirubin level was 5.14 mg/dL, the direct bilirubin level was 2.85 mg/dL, the blood urea nitrogen level was 39 mg/dL, and the creatinine level was 1.26 mg/dL. The baby had widespread ecchymosis on its body (Fig. 2). By abdominal ultrasound, pericholecystic minimal oedema and perihepatic fluid were detected. By trans-fontanel ultrasound, subependymal bleeding was detected, and the third and lateral ventricles were found to be depressed. The baby died because of massive bleeding. A CCHF virus PCR was positive, CCHF IgM was negative and IgG was positive according to ELISA.

Second case

A pregnant woman at 19 weeks of gestation was admitted to the hospital. Her complaints were fever, malaise, headache, myalgia, nausea, vomiting, diarrhoea, and subconjunctival bleeding (Table 1). No pathological sign was detected by obstetric ultrasound. On the fourth day of hospitalization, the WBC count was 6800/mm^3, the PLT count was 115 000/mm^3, the Hb level was 10.3 g/L, the AST level was 186 IU/L, the ALT level was 105 IU/L, and the lactate dehydrogenase level was 378/IU/L. The PLT count was decreased to 53 000/mm^3. Ribavirin was not given. The patient was discharged. In serological analysis, anti-CCHF virus IgM was found to be positive, and CCHF virus was detected by PCR (Table 2). At the 22nd week of gestation, obstetric ultrasound revealed fetal intra-abdominal fluid, and an amniocentesis was performed (Fig. 2a). The serological and PCR analyses of the amniotic fluid gave negative findings. The risk of fatal delivery

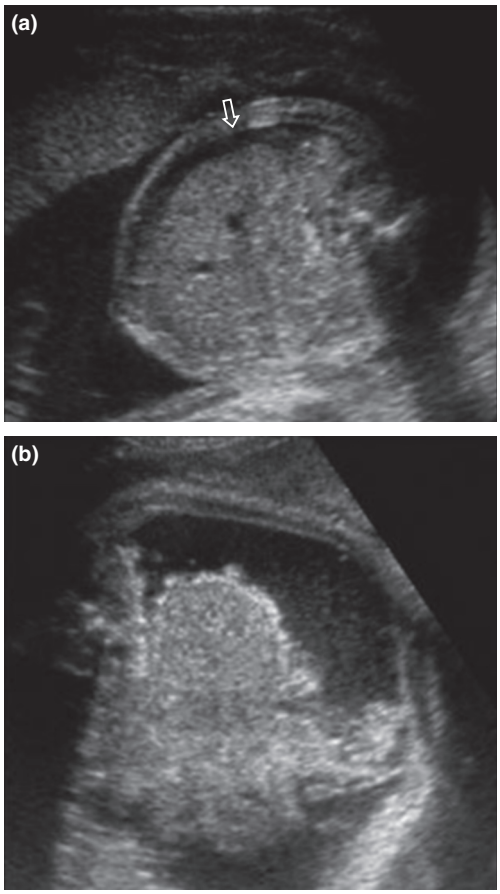

FIG. 2. Ultrasound image of the second case. (a) Fetal intra-abdominal fluid. (b) At the 38th week of gestation, there is an increase in the amount of fetal intra-abdominal fluid.

was explained to the family. Fetal intra-abdominal fluid was found to be increased and a hydrocele was detected at the 38th week of gestation; this finding was related to bleeding or perforation (Fig. 2b).

When the baby was delivered, it was heavily stained with meconium. It was resuscitated and then operated on with the diagnosis of necrotizing enterocolitis (NEC). The WBC count was 17 100/mm^3, the Hb level was 15.2 g/L, the PLT count was 219 000/mm^3, the AST level was 83 IU/L, the ALT level was 23 IU/L, the total protein level was 4.3 g/dL, the albumin level was 2.4 g/dL, the prothrombin time was 17.5 secs, the activated partial prothrombin time was 37.3 secs, and the international normalized ratio was 1.45. Treatment with broad-spectrum antibiotics was started. *Enterobacter agglomerans* was isolated from blood culture. On the fifth day, the temperature was 38.5°C, the WBC count was 4400/mm^3, the Hb level was 3 g/L, and the PLT count was 32 000/mm^3. The baby died because of massive nasal, intrathechal and gastrointestinal bleeding. Anti-CCHF virus IgM and PCR were negative; IgG could not be tested for.

Third case

A pregnant woman at 28 weeks of gestation was admitted to the hospital with abdominal pain, dyspnoea, epistaxis, and haematemesis. She was tachycardic (112/min) and her abdomen was sensitive. Pleural effusion was noted on her chest X-ray. By ultrasound, the fetus was observed to be alive and compatible with 28 weeks of development; there were no placental or retroplacental pathological signs. As preterm delivery action was considered, betamethasone was started. Ribavirin was not given, because of contraindications during pregnancy. Forty units of PLTs, 24 units of fresh frozen plasma and 5 units of erythrocyte suspension were given. On the third day of hospital admission, the patient had convulsions, probably because of intracranial bleeding. The baby could not be delivered, and died with the mother. PCRs for CCHF virus and anti-CCHFvirus IgM were found to be positive.

Discussion

CCHV is an endemic fatal infection in Africa, Asia, Eastern Europe, and the Middle East [1]. The presence of fever, malaise and headache concomitant with laboratory findings of leukopenia, thrombocytopenia and elevation of AST, ALT, CPK and LDH levels is a common clinical picture in CCHF. Intrauterine acquisition has been reported for other viral haemorrhagic fevers, such as Dengue infection [4,5]. Horizontal transmission of the CCHF virus from a mother to her child has been reported before [6], but intrauterine acquisition of CCHF has not yet been described. This is the first report of various forms of intrauterine infection with CCHF virus.

Among three pregnant women, history, clinical features, complete blood counts and biochemical test results were compatible with CCHF virus infection, and the diagnoses were confirmed by PCR and ELISA. Two of the three pregnant women delivered their babies at term, and their babies died because of massive bleeding within the first 5 days after delivery. In one of these two babies, CCHF virus was confirmed by PCR and ELISA. However, in the other baby, the laboratory diagnosis was not confirmed. One fetus died with the mother (Table 2).

There could be either intrauterine or perinatal transmission of the infection in pregnancy. The baby of the first case probably acquired the infection by either intrauterine or perinatal transmission. The mother was infected at the term. The clinical and laboratory findings of the newborn were compatible with CCHF virus infection, and it died because of massive bleeding; the PCR was positive. In endemic areas,

CCHF infection should be differentiated from HELLP syndrome, which develops in approximately 4–12% of women with severe pre-eclampsia or eclampsia at the end of pregnancy [7,8]. In CCHF infection, the haemolytic anaemia is not seen, and leukopenia is common, whereas in the patients with HELLP syndrome, haemolytic anaemia is seen and leukopenia is not [3].

The mother in the second case had the infection at a relatively early phase (18th week) of intrauterine development. She was cured. She delivered the baby at term, but although she was cured of CCHF, the baby developed NEC after the delivery. This could indicate intrauterine infection at the fourth month (second trimester). CCHF should be considered in the aetiology of NEC among newborns. Several factors, such as infectious agents/toxins, enteral alimentation, mesenteric ischaemia/tissue hypoxia, and prematurity, appear to play either a primary or a secondary role in the development of NEC [9–11]. The onset of NEC rarely occurs in the first 3 days of life. Therefore, the presence of NEC during delivery was considered to be due to intrauterine CCHF virus infection.

The third mother aborted her baby during the disease, indicating that intrauterine CCHF virus infection could have caused the abortion.

Healthcare workers and care-givers in endemic areas should apply appropriate standard precautions to prevent secondary transmission of CCHF virus. As standard precautions, masks, gloves and gowns will be sufficient for protection from blood and body fluids of CCHF patients [12].

In conclusion, CCHF virus infection among pregnant women may result in abortion or neotanal complications and death. The result is closely related to the term of the pregnancy as well as the severity of the illness of the mother. Transmission of CCHF virus could be either intrauterine or perinatal. In endemic regions, CCHF virus infection should be considered in the differential diagnosis of HELLP syndrome, and obstetricians should be familiar with CCHF virus infection. In the aetiology of NEC, CCHF should be considered.

Transparency Declaration

The authors have no conflict of interest.

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