

Crimean-Congo hemorrhagic fever in pregnancy: A systematic review and case series from Russia, Kazakhstan and Turkey



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ABSTRACT

Background: Crimean–Congo hemorrhagic fever (CCHF) is acute viral infection and a major emerging infectious diseases threat, affecting a large geographical area. There is no proven antiviral therapy and it has a case fatality rate of 4–30%. The natural history of disease and outcomes of CCHF in pregnant women is poorly understood.

Objectives: To systematically review the characteristics of CCHF in pregnancy, and report a case series of 8 CCHF cases in pregnant women from Russia, Kazakhstan and Turkey.

Methods: A systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement protocol. PubMed, SCOPUS, Science Citation Index (SCI) were searched for reports published between January 1960 and June 2016. Two independent reviewers selected and reviewed studies and extracted data.

Results: Thirty-four cases of CCHF in pregnancy were identified, and combined with the case series data, 42 cases were analyzed. The majority of cases originated in Turkey (14), Iran (10) and Russia (6). There was a maternal mortality of 14/41 (34%) and fetal/neonatal mortality of in 24/41 cases (58.5%). Hemorrhage was associated with maternal ($p=0.009$) and fetal/neonatal death ($p<0.0001$). There was nosocomial transmission to 38 cases from 6/37 index pregnant cases.

Conclusion: Cases of CCHF in pregnancy are rare, but associated with high rates of maternal and fetal mortality, and nosocomial transmission.

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Introduction

Crimean-Congo hemorrhagic fever (CCHF) is an acute tick-borne viral infection and a major emerging infectious diseases threat. It affects a wide geographical area, centered in Eurasia including Turkey, Russia and Kazakhstan but is under-reported and diagnosis is often delayed. Fever, thrombocytopenia and

hemorrhage are the characteristic clinical features, with supportive care forming the mainstay of treatment protocols, although ribavirin is utilized by some centers. Provision of blood product support and access to critical care interventions can improve outcomes, with reported case fatality rates (CFR) being 4–20%.¹

The majority of cases of CCHF report a history of tick bite, but healthcare related transmission of CCHF is well reported, and occurs in both high and low-resource settings. Failure to recognize CCHF and as a result implement appropriate infection, prevention and control procedures results in significant nosocomial risk, especially in the context of critical care

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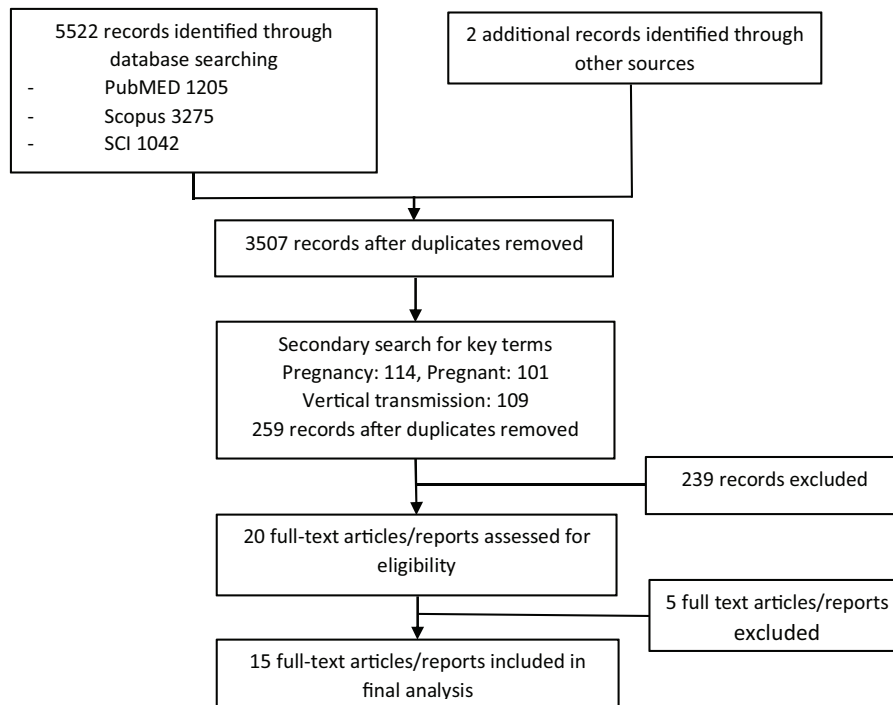


Figure 1. Flowchart of literature search.

interventions.^{2–4} Retrospective analysis from Turkey has demonstrated that needle stick injuries are the most frequent cause of high risk exposures, followed by ‘splash’ exposures to mucous membranes and highlighted a potential benefit of ribavirin post-exposure prophylaxis.⁵

Although the immune system changes in pregnancy are not completely understood, pregnant woman may be more likely to acquire certain infectious diseases such as toxoplasmosis, and be more severely affected by others such as influenza and varicella.⁶ Viral hemorrhagic fevers such as Ebola virus disease and Lassa Fever are more severe in pregnancy,^{7,8} and frequently result in spontaneous abortion with additional nosocomial risk. Although clinical and epidemiological CCHF data are increasingly reported, few data exist on CCHF in pregnancy.^{9–11} The mortality of CCHF disease in pregnant women appears to be higher than in the general population (up to 33%),¹⁰ and the severe course of CCHF in pregnant women may also increase risk of nosocomial infection in health care settings.²

In this study we aimed to systematically review the characteristics of CCHF cases in pregnancy, and to report an additional case series of 8 CCHF cases in pregnant women from Russia, Kazakhstan and Turkey.

Material and methods

We planned and reported this systematic review in accordance with guidelines for performing and reporting systematic reviews and meta-analyses (PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses). We searched PubMed, Science Citation Index (SCI) and Scopus databases for English and foreign language studies published between January 1960 and June 2016. The keyword ‘Crimean Congo H(a)emorrhagic Fever’ was utilised then combined with ‘pregnancy’; ‘pregnant’ and ‘vertical’. We also searched reference sections; Google scholar and reviews for other studies. Statistical analyses were performed with the use of IBM SPSS Statistics for Windows; Version 24.0. Armonk; NY: IBM Corp.

Study Selection

Two reviewers (HL & IB) independently screened the titles and abstracts of all studies that were identified through database searches. Inclusion criteria were (1): report of a case of laboratory confirmed Crimean-Congo Hemorrhagic fever OR report of a clinical case with a direct epidemiological link to a laboratory confirmed case of Crimean-Congo hemorrhagic fever and (2); pregnancy. Full-text copies of potentially relevant studies were retrieved and reviewed independently (TF & IB), extracting data from each study meeting inclusion criteria. Standardised data was extracted from each case when available including date, age, gestation, laboratory diagnosis, outcome of mother and foetus, hemorrhagic manifestations and secondary cases.

Results

The initial search results identified the following number of records: Scopus 3275; PubMed 1205; and SCI 1042. After removal of duplicates 3507 records were combined with secondary search terms (Pregnancy: 101, pregnant:114, vertical:109). An additional search by Google scholar identified 2 further reports. 20 full text articles were then retrieved, with the total number of 34 CCHF cases identified in pregnancy in 15 articles (Figure 1). An additional 8 cases were added from this case series from Russia (5 cases), Kazakhstan (2 cases) and Turkey (1 case), resulting in total of 42 cases of CCHF in pregnancy (Table 1).

The first report was from a case in 1979 and the last case occurred in 2016, with cases from Turkey (14 cases), Iran (10 cases), Russia (6 cases), former Yugoslavia (4 cases), Iraq (3 cases), Kazakhstan (2 cases), Mauritania (2 cases) and Bulgaria (1 case). Gestation was reported in 29 cases, with 11 cases occurring in the first 20 weeks of pregnancy and 18 cases occurring in the second 20 weeks of pregnancy.

Maternal and fetal/neonatal outcome was reported in 41 cases, with 14/41 cases (34%) reporting maternal death, and foetal/neonatal death occurring in 24/41 cases (58.5%). In the first

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