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REVIEW

Hantavirus Infection during Pregnancy

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Abstract

Hantavirus infection is a global health challenge, causing widespread public concern. In recent years, cases of hantavirus infection in pregnant women have been reported in many countries. The infected pregnant women and their fetuses appear to have more severe clinical symptoms and worse clinical outcomes. Hence, to study the prevalence of hantavirus infection in pregnant women, this study will focus on the epidemiological distribution of the virus, different virus species penetrating the placental barrier, and factors affecting the incidence and clinical outcome of the infection in pregnant women and their fetuses. In addition, this review will also discuss the diagnostic tools and treatments for pregnant patients and provide an overview of the relevant future research.

Keywords Hantavirus · Pregnancy · Hantaan virus (HTNV) · HPS · HFRS

Introduction

Hantaviruses are negative-sense, single-stranded, enveloped RNA viruses belonging to the family *Hantaviridae*. Since the first hantavirus was isolated in 1978, many countries and regions have reported a series of hantavirus infections continuously (Lee *et al.* 1978). Hantaviruses cause two clinical syndromes in humans; designated hemorrhagic fever with renal syndrome (HFRS), and hantavirus cardiopulmonary syndrome (HPS). HFRS mostly occur in Eurasian countries, caused by Hantaan virus (HTNV), Seoul virus (SEOV), Puumala virus (PUUV) and Dobrava virus (DOBV) (Avsic-Zupanc *et al.* 2019). The clinical features of HFRS are severe systemic manifestations, including fever, hemorrhage and acute renal failure. HPS is mainly a group of syndromes with respiratory system involvement, caused by Sin Nombre virus (SNV), Andes virus, and other viruses. The leading cause of death in HPS is acute progressive non-cardiogenic pulmonary edema and respiratory failure (Peters *et al.* 1999).

Hantaviruses are zoonotic viruses that can be carried by small rodents. Approximately 20,000 cases of hantavirus-related diseases occur worldwide each year (Jiang *et al.* 2017). Furthermore, there is a clear indication that the incidence rate increases every year (Jiang *et al.* 2017; Watson *et al.* 2014). The mortality rates reported are 12% for HFRS and 60% for HPS (Zhang *et al.* 2010; Jonsson *et al.* 2010). Pregnant women are afflicted by inhalation of host secretions and excretions carrying the virus, or by exposure to rodent carriers (Pedrosa and Cardoso 2011). However, the cases of women infected with hantavirus during pregnancy are rarely reported even in areas where hantaviruses are concentrated, which poses certain difficulties for subsequent research and clinical management. Here, in order to contribute to the diagnosis, treatment, and prognosis prediction, we reviewed past cases of hantavirus infections in pregnant women.

Hantavirus Infection during Pregnancy

Global Distribution of Hantavirus Infection during Pregnancy

As reported in the existing literature, pregnant women with hantavirus infection mainly live in areas where hantaviruses are prevalent. Almost every pregnant woman infected with hantaviruses during pregnancy has a clear history of exposure to the epidemic area (Fig. 1).

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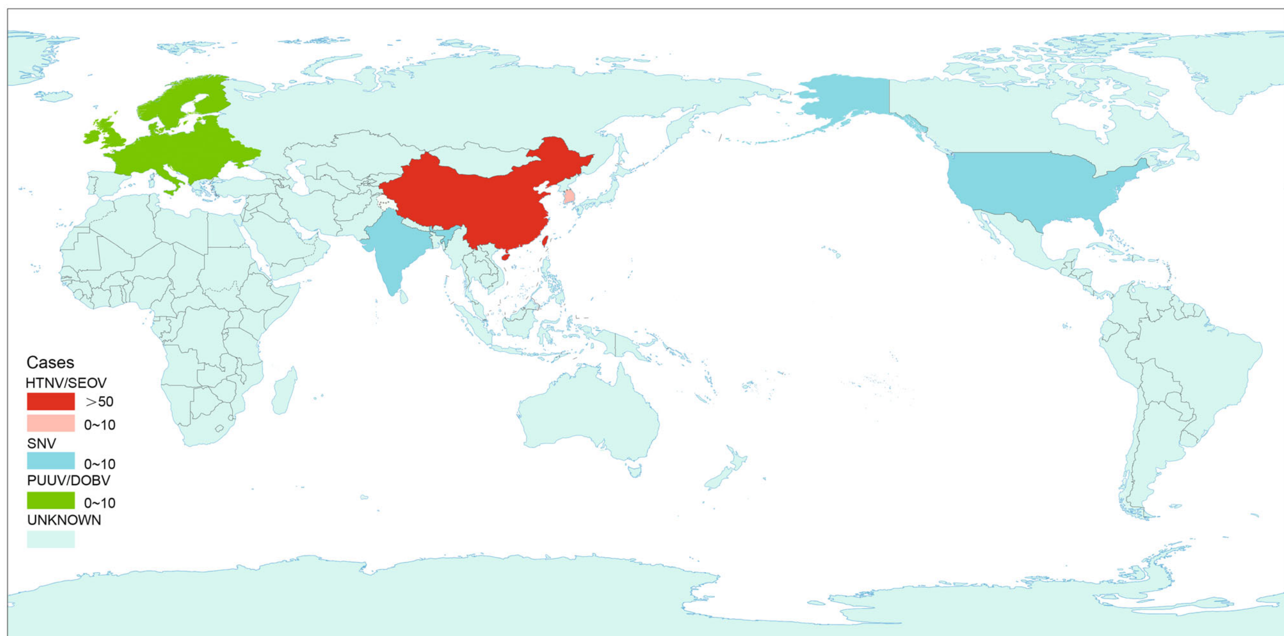

Fig. 1 Global geographic distribution of pregnant women with hantavirus infection.

Therefore, the epidemiological distribution primarily relies on the rodent host distribution, and it is influenced by factors such as the climate, environment, and food availability, which can make up a unique rodent host-hantavirus system. The rodent hosts of principal disease-causing hantaviruses are *Apodemus agrarius* (HTNV) in Asia, *Myodes glareolus* (PUUV) in Europe, and *Peromyscus maniculatus* (SNV) in the Americas (Watson *et al.* 2014; Kariwa *et al.* 2007; Vaheri *et al.* 2013).

Incidence and Clinical Outcomes of Different Hantavirus Species during Pregnancy

Cases of pregnant women infected by HTNV and SEOV hantaviruses are more than that infected by other hantavirus species (Fig. 1, Table 1). This is related to the high incidence rate and large population in the areas where these two virus species are primarily distributed. China and South Korea are the top two hantavirus infection areas (Kariwa 2017), and this is consistent with the distribution of their rodent hosts, which is also in line with the final findings of this review.

Hantavirus infection with different species during pregnancy also has different results for pregnant women. As observed from our statistical review, the mortality rate of pregnant women infected with HTNV/SEOV was 10.5% (27/256) (Table 1), and that of those infected with SNV was 25.0% (2/8) (Table 1). From the data we collected, the mortality rate of pregnant women infected with HTNV was not significantly different from that of the general

Table 1 Clinical outcomes of pregnant women infected with different species of hantaviruses.

Virus species	Outcomes of pregnant women after infection			Total cases
	Deaths	Survive but have sequelae	Survive without sequelae	
HTNV/SEOV	27	20	209	256
PUUV	0	0	10	10
SNV	2	0	6	8
DOBV	0	0	2	2
Total cases	29	20	227	276

The sequelae mainly include menstrual disorders, amenorrhea, no milk secretion after delivery, sexual dysfunction, hair loss, autonomic dysfunction, and chronic renal insufficiency (Hofmann *et al.* 2012; Ji *et al.* 2017; Howard *et al.* 1999; Partanen *et al.* 1990; Silberberg *et al.* 1993; Prebensen 1997; Tiilikainen and Jouppila 1989; Jing and Jing 1994; Wang *et al.* 1992; Sha *et al.* 2000; Mace *et al.* 2013; Dai 2004; Liu *et al.* 2013; Georges *et al.* 2008; Schneider *et al.* 2009; Gilson *et al.* 1994; Murthy *et al.* 2016; Wang 2014; Zhang 1995; Duan *et al.* 1996; Kim and Choi 2006; Zheng 1985; Cui 2005; Liu *et al.* 2017; Todorovic *et al.* 2010; Chen 2008; Xie 1994; Hao 1997; Ying 1984; Gao 2013; Chen 1994; Lu *et al.* 2018; Li 2019; Ma *et al.* 2003; Latus *et al.* 2013).

population, while that of those infected with SNV was lower than that of the general population (Zhang *et al.* 2010; Jonsson *et al.* 2010). We speculate that the sample size may primarily limit this. Moreover, after being infected by a hantavirus, the residual sequelae, which mainly consist of menstrual disorders, amenorrhea, no milk secretion after delivery, sexual dysfunction, hair loss, autonomic dysfunction and chronic renal insufficiency, were only seen with HTNV/SEOV infections (Table 1). Furthermore, no deaths have been reported in pregnant women infected with PUUV or DOBV (Hofmann *et al.* 2012; Ji *et al.* 2017; Partanen *et al.* 1993). However, PUUV and DOBV cannot be ruled out due to the limited number of cases (Table 1).

The clinical outcome for fetuses is also significantly different. Since the death of the mother causes the death of the fetus in most cases, this review will only discuss the cases where the mother survived the hantavirus infection. According to the available data, fetal deaths were only reported in HTNV/SEOV and SNV infections (Table 2). The mortality rate of fetuses delivered by pregnant women with HTNV/SEOV infections was 31.8% (71/223) (Table 2), and that of those delivered by pregnant women with SNV was 33.3% (2/6) (Table 2). Also, several sequelae, including congenital heart disease, necrotizing enteritis, restricted growth and development, as well as hydrocephalus, troubled these babies (Table 2). The incidence rate of sequelae in the babies, whose mothers had been infected with HTNV/SEOV and SNV was 3.6% (8/223) and 16.7% (1/6), respectively (Table 2).

Placental Passability and Hantavirus Species

There were no reports of fetal malformations in pregnant women with a hantavirus infection, though many vertically transmitted viral infections are likely to cause fetal malformations (Seferovic *et al.* 2018; Silasi *et al.* 2015).

Currently, there is no evidence that PUUV, DOBV and SNV can be transmitted through the placenta (Hofmann *et al.* 2012; Partanen *et al.* 1993; Howard *et al.* 1999). Partanen *et al.* (1990) presented a case, where a 29 year-old woman at 17 weeks gestation had suffered from acute abdominal pain with high fever and myalgia. As a result, she had been diagnosed with PUUV infection. After treatment, the woman had recovered within 4 weeks and delivered a healthy boy naturally. Besides, the postoperative serological testing showed no evidence of placental transmission. However, few cases of fetal death caused by PUUV infection were also reported (Partanen *et al.* 1993; Silberberg *et al.* 1993; Prebensen 1997; Tiilikainen and Jouppila 1989). Hofmann *et al.* (2012) conducted an immunological and molecular analysis of hantaviruses in the cord blood of four pregnant women, who had been infected with PUUV or DOBV. The results also showed no evidence of virus transmission through the placenta. Howard *et al.* (1999) reviewed five cases of HPS during pregnancy, and as expected, there was no evidence of vertical transmission, though SNV infections mostly had severe consequences, even death, in pregnant women and fetuses.

Therefore, it could be speculated that HTNV and SEOV pass through the placental barrier. Liu *et al.* (1987) suggested that there is a phenomenon of vertical transmission between the mother and the baby. Nonetheless, no evidence directly proves it. Lee (1989) detected the presence of IgM antibody against HTNV in the blood of fetuses, whose mothers had a HTNV infection, confirming the possibility of placental transmission. Kim *et al.* (1978) studied a pregnant woman, who had had a miscarriage due to hypotension after SEOV infection. After the autopsy of the fetus, researchers found bleeding throughout the body, including lungs, kidneys, and adrenal glands. This is in line with the symptoms of SEOV infection, but unfortunately, they did not perform further serological testing of the fetus

Table 2 Effects of infections with hantavirus species in pregnant women on their fetuses.

Virus species	Outcomes of fetuses			Total cases
	Deaths	Survival with sequelae	Survival without sequelae	
HTNV/SEOV	71	8	144	223
PUUV	0	0	9	9
SNV	2	1	3	6
DOBV	0	0	2	2
Total cases	73	9	158	240

The sequelae mainly include congenital heart disease, necrotizing enteritis, restricted growth and development, and hydrocephalus (Hofmann *et al.* 2012; Ji *et al.* 2017; Howard *et al.* 1999; Partanen *et al.* 1990; Silberberg *et al.* 1993; Prebensen 1997; Tiilikainen and Jouppila 1989; Jing and Jing 1994; Wang *et al.* 1992; Sha *et al.* 2000; Mace *et al.* 2013; Schneider *et al.* 2009; Gilson *et al.* 1994; Wang 2014; Zhang 1995; Duan *et al.* 1996; Kim and Choi 2006; Todorovic *et al.* 2010; Chen 2008; Xie 1994; Hao 1997; Ying 1984; Chen 1994; Lu *et al.* 2018; Li 2019; Ma *et al.* 2003; Latus *et al.* 2013).

(Kim *et al.* 1978). In addition Jing PT and Jing H (1994), isolated hantaviruses from fetal brain tissues of an aborted fetus. Unexpectedly, the results indicated that hantaviruses could pass not only the placental barrier but also the blood–brain barrier. However, it is a pity that the study failed to identify the species. Instead, it was based on the epidemiological analysis of the target area, which indicated that the virus was most likely SEOV. Most of the abortion and stillbirth cases in patients with HFRS occur when they have a fever, so further research is needed to clarify the specific mechanism (Chen 1994; Wang *et al.* 1992; Sha *et al.* 2000).

Influence of Age on the Clinical Outcome

The clinical outcomes of pregnant women with a hantavirus infection are also related to their age. The mortality rate of women aged 30 or older and infected with hantaviruses during pregnancy is 45.5% (5/11) (Table 3), while for women under 30, it is only 2.5% (1/40) (Table 3). Hjertqvist *et al.* (2010) found, in a study with 5,282 patients, that there is a significant correlation between mortality and the age of the hantavirus-infected patients. The mortality rates of pregnant women and others increase with age, and the trend remains consistent.

Incidence and Gestation

The incidence of hantavirus infection in pregnant women varies in different gestational periods. By reviewing the literature, we conducted a statistical analysis of the gestational age of women with a hantavirus infection during pregnancy. Among the reported cases of hantavirus-infected pregnant women, the incidence rate in the first trimester (< 13 weeks) was 7.7% (4/52) (Table 3), whereas that in the second trimester (≥ 13 weeks, < 28 weeks) and the third trimester (≥ 28 weeks) was 92.3% (48/52) (Table 3). Coincidentally, this phenomenon was also found in other placenta-transmissible viruses. Zhao (2017) conducted a controlled observation, including 288 cases of HPV-infected pregnant women at different stages of pregnancy, and found that the incidence of viral infection was the highest at the third stage. Moreover, having researched Epstein-Barr virus infection in pregnant women at different stages of pregnancy, Ming (2017) also reached the same conclusion.

Delivery Mode and the Outcome of the Fetus

Different mode of delivery may exert various influences on the transmission of the virus from mother to child. Lee (1989) detected hantaviruses in the serum of a vaginally delivered fetus. The fetus died within 12 h of delivery. However, there were no similar cases reported in fetuses born via cesarean section.

Diagnosis and Treatment

Early diagnosis is vital for pregnant women with a hantavirus infection since it leads to early and more effective treatment, as well as a better clinical outcome. Accurate diagnosis usually relies on clinical manifestations and laboratory tests. Exploring the history of exposure in the epidemic area is also essential for a precise diagnosis. The typical clinical manifestations of HFRS are fever, hemorrhage, hyperemia, hypotensive shock and kidney damage accompanied by clinical symptoms, such as hematuria, proteinuria, and disseminated intravascular coagulation (DIC) (Lazzerini *et al.* 2017). Similar to the general population, the typical clinical course of HFRS in pregnant women is divided into the following: Fever period (3–7 days), hypotensive period (hours to 2 days), oliguria (3–7 days), polyuria (several days to weeks), and recovery period (2–3 months) (Vaheri *et al.* 2013; Latus *et al.* 2015; Connolly-Andersen *et al.* 2014). The clinical symptoms of HPS include flu-like symptoms in the prodromal stage (5 days), subsequent acute respiratory distress syndrome (ARDS), bilateral diffuse interstitial pulmonary edema, respiratory failure, as well as non-cardiogenic shock (Duchin *et al.* 1994; Khan *et al.* 1996; Hallin *et al.* 1996; Macneil *et al.* 2011). Molecular, immunochemical, and serological examination contribute to routine laboratory tests (Zou *et al.* 2016). IgM/IgG antibodies against the Gn and Gc of hantaviruses are often used to aid the diagnosis (Hedman *et al.* 1991).

However, early diagnosis is not that simple and straightforward, although diagnostic criteria are clear. Misdiagnosis often happens because of inexperienced non-specialist clinicians, a limited number of cases, and atypical clinical manifestations. Misdiagnosis rate of pregnant patients with HFRS infection is as high as 50% according to several reports (Xia 2009; Yun 2007). Patients with HFRS that have mild or atypical presentations are most likely to be misdiagnosed, especially in the early period (Xia 2009; Yun 2007). Pregnant women with a hantavirus infection are often misdiagnosed with acute fatty liver of pregnancy (AFLP), hemolysis, and elevated liver enzymes and low platelets (HELLP), as they have similar clinical manifestations (Mace *et al.* 2013; Haram *et al.* 2009). Thus, accurate differential diagnosis is vital. A substantial reduction in non-selective proteinuria in a short period is conspicuous for HFRS, but rare for AFLP and HELLP (Clement *et al.* 2013).

Currently, there is no safe and effective treatment for pregnant women with hemorrhagic fever. Recently, new

Table 3 Effects of the age and gestation period on pregnant women with hantavrirus infection.

Case	Age (year)	Gestation (week)	Delivery	Mother's outcome	Fetal outcome	Deformity (yes/no)
Kim and Choi (2006)	27	15	VD	Recovered without sequelae	Survived and healthy	No
Kim *et al.* (1978)	27	28	–	Recovered after hemodialysis	Died	No
Chun *et al.* (1992)	26	18	CS	Recovered without sequelae	Survived and healthy	No
	25	19	VD	Recovered without sequelae	Survived and healthy	No
Lee (1989)	28	29	VD	Recovered without sequelae	Died 11 h after birth	No
Kim *et al.* (1997)	29	27	CS	Recovered without sequelae	Survived and healthy	No
Park *et al.* (1998)	27	29	VD	Recovered without sequelae	Survived and healthy	No
Choi *et al.* (2000)	29	30	CS (Mechanical Ventilation)	Recovered after emergency CS	Fetal growth restriction with respiratory distress	No
Liu *et al.* (2017)	24	39	CS	Recovered without sequelae	Survived and healthy	No
Todorovic *et al.* (2010)	23	23	VD	Recovered without sequelae	Survived and healthy	No
	29	26	VD	Recovered without sequelae	Survived and healthy	No
Zheng (1985)	26	32	–	Died	–	–
Chen (2008)	30	34	VD	Recovered without sequelae	Survived and healthy	No
Xie (1994)	34	28	–	Died of uremia	–	–
	25	20	–	Recovered without sequelae	Died	No
Hao (1997)	30	29	–	Died	Died	–
Ying (1984)	20	36	VD	Recovered without sequelae	Died	–
Gao (2013)	22	32	Unknown	Recovered without sequelae	Unknown	Unknown
Hofmann *et al.* (2012)	38	14	VD	Recovered without sequelae	Survived and healthy	No
	23	28	VD	Recovered without sequelae	Survived and healthy	No
	40	22	VD	Recovered without sequelae	Survived and healthy	No
	33	28	CS	Recovered without sequelae	Premature birth	No
Georges *et al.* (2008)	29	6	Unknown	Recovered without sequelae	Unknown	Unknown
Partanen *et al.* (1990)	29	17	VD	Recovered without sequelae	Survived and healthy	No
Prebensen (1997)	28	10	VD	Recovered without sequelae	Survived and healthy	No
Howard *et al.* (1999)	25	29	VD	Recovered without sequelae	Died	No
	34	13	–	Died	Died	No
	20	20	VD	Recovered without sequelae	Survived and healthy	No
	27	17	VD	Recovered without sequelae	Survived and healthy	No
	28	16	Unknown	Recovered without sequelae	Died	No
Latus *et al.* (2015)	36	23	Unknown	Recovered without sequelae	Survived and healthy	No

Table 3 (continued)

Case	Age (year)	Gestation (week)	Delivery	Mother's outcome	Fetal outcome	Deformity (yes/no)
Ma *et al.* (2003)	29	–	VD	Recovered without sequelae	Died	No
Ji *et al.* (2017)	24	22	VD	Recovered without sequelae	Died	No
	22	23	CS	Recovered without sequelae	Survived and healthy	No
	28	13	VD	Recovered without sequelae	Survived and healthy	No
	34	21	–	Recovered without sequelae	Terminated of pregnancy	No
Wang (2014)	26	24	Unknown	Recovered without sequelae	Died	No
	26	27	Unknown	Recovered without sequelae	Premature birth and died	No
	31	7	Unknown	Died	Died	No
	24	21	Unknown	Recovered without sequelae	Unknown	No
	21	32	Unknown	Recovered without sequelae	Premature and suffered from congenital heart disease and necrotizing enteritis	No
	27	31	Unknown	Recovered without sequelae	Survived and healthy	No
Mace *et al.* (2013)	Mid-20s	26	CS	Recovered without sequelae	Premature birth and respiratory distress	No
Cui (2005)	28	32	Unknown	Recovered without sequelae	Unknown	Unknown
Dai (2004)	29	32	Unknown	Recovered without sequelae	Unknown	Unknown
Liu *et al.* (2013)	28	36	CS	Recovered without sequelae	Survived and healthy	No
Li (2019)	28	36	Unknown	Recovered without sequelae	Unknown	Unknown
Schneider *et al.* (2009)	25	36	CS	Recovered without sequelae	Survived but respiratory distress	No
Gilson *et al.* (1994)	25	29	VD	Recovered without sequelae	Survived but pulmonary hemorrhage	No
	20	20	Unknown	Recovered without sequelae	Unknown	Unknown
Murthy *et al.* (2016)	30	Unknown	VD	Died	Unknown	Unknown
Nowakowska *et al.* (2009)	32	10	Unknown	Unknown	Unknown	Unknown

Sequelae: It refers to the remaining symptoms in pregnant women infected with hantavirus after their condition improves, which are mentioned in Tables 1 and 2.

CS cesarean section, *VD* vaginal delivery.

treatments have been developed, and satisfying medical results have been achieved. For example, pregnant women with a hantavirus infection during pregnancy can benefit from symptomatic treatment and supportive care, mainly including diuresis, hemodialysis, oxygen therapy, shock therapy, liver protection therapy and liquid therapy. However, increased cardiac load during pregnancy and pulmonary capillary damage caused by the hantavirus infection are more likely to cause ARDS and heart failure. Hence, it is essential to control the infusion rate during oliguria (Chen 1994). Furthermore, continuous renal replacement therapy (CRRT) plays a leading role, especially if hantavirus-infected pregnant patients display high blood volume and pulmonary edema (Ji *et al.* 2017). Last but not the least, glucocorticoids have strong anti-inflammatory effects and are widely used in patients with stubborn and unresolved renal failure. However, the question that needs to be studied further is whether glucocorticoids can improve the health of the patients (Kruger *et al.* 2015; Martinuč Bergoč *et al.* 2013).

In areas with high hantavirus prevalence, vaccination of women before pregnancy can effectively alleviate hantavirus infections (Dai 2004; Liu *et al.* 2013). However, for those who are already pregnant, the safety and effectiveness of vaccination have not been insightfully studied (Dai 2004; Liu *et al.* 2013).

Summary

Although there are not many cases of hantavirus infection reported in pregnant women, even in the endemic areas, clinicians are expected to thoroughly consider severe consequences when they receive patients with similar symptoms. Specific immune status of pregnant women might increase their susceptibility to hantavirus infection. Pregnant women have unique immunology and physiology, and their immune system can develop a particular immunosuppressive state by suppressing cellular immunity to tolerate fetal antigens of paternal origin (Beigi 2017; Jamieson *et al.* 2006). However, maintenance of this specific immune state during pregnancy has not been thoroughly explored. Gaunt and Ramin (2001) believe that this immunosuppressive state might be closely related to factors such as the absence of MHC-I antigens, the presence of unique HLA surface molecules, and nonspecific reduction of systemic immunoreactivity. Moreover, the blocking antibody, expressions of complement regulatory proteins, and reduced immunoreactivity might contribute to the formation of this unique immune state. These changes are likely to influence a systemic immune response to infections and lead to increased susceptibility to hantavirus infection.

After being infected with hantavirus, pregnant women and their fetuses seem to have worse clinical symptoms and outcomes (Sha *et al.* 2000; Liu *et al.* 2003) Nevertheless, currently, no theory can entirely explain the mechanism behind this phenomenon. In similar research of other viruses, this phenomenon is attributed to the unique immunological and physiological characteristics of pregnant women (Beigi 2017; Beigh 2012). However, patients' immune response to a hantavirus infection, such as cytokine storms, is likely to harm the body (Schönrich *et al.* 2008). Pregnant women are in a specific state of immunosuppression, and their immune damage is much smaller than that of other people, which is inconsistent with the findings of this literature review. Therefore, it can be speculated that the cause for this difference might come from two aspects. Primarily, pregnancy increases the organ burden of patients with a hantavirus infection, worsens the health, and increases the risk of death (Guimarães *et al.* 2019). Additionally, the flow dynamics of patients might change during pregnancy. Consequently, the synthesis of clotting factors increases, and the placenta synthesizes a large number of thrombogenic substances (Avsic-Zupanc *et al.* 2019).

Early and timely diagnosis, comprehensive symptomatic treatment based on liquid therapy, and accurate judgments improve the patient's life (Dai 2004). Moreover, the cooperation between emergency room physicians, infectious disease specialists, and obstetricians is also helpful for timely diagnosis and treatment. These measures are expected to improve the health of pregnant women and fetuses to a great extent.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Animal and Human Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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