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Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infections in pregnancy – An overview

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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infections, like most other viruses that affect the respiratory tract can cause severe maternal illness and adverse pregnancy outcomes. They are not only highly transmissible (acquired through droplets), but Host reservoirs such as dromedary camels for MERS-CoV and masked palm civet for SARS-CoV-1 are critical links in the onset of outbreaks. Clinically they present with flu-like symptoms and therefore a high index of suspicion is required to ensure timely diagnosis and tailored management. Although there are not many reported series on these infections in pregnancy they seem to be associated with an increased risk of preterm delivery and maternal mortality. Diagnosis is made by PCR from nasopharyngeal swabs. There are currently no effective anti-viral agents for these viruses but following infections various agents have been administered to patients. The most important aspect of management should be early identification of deterioration and intensive support and prevention of transmission. Our understanding of the evidence of the impact of both infections on pregnancies suggests the potential for future repeat outbreaks, hence the importance of maintaining vigilance across healthcare systems.

Introduction

The last published case reports, case series and epidemiological studies on SARS-CoV-1 and MERS were in 2004 and 2018 respectively. As SARS-CoV-1 and MERS belong to the same family as the etiological agent of the current pandemic (COVID-19), this review is a reminder of the differences and similarity between them.

Coronaviruses are single stranded RNA viruses from the subfamily *Coronavirinae* in the *Coronaviridae* family with significant propensity for genetic variation because of their large RNA genome [1–3]. The name 'coronavirus' derives from their crown-like morphology. They have been associated with infections in animals, human and birds. Four genera of coronaviruses are described: *Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus*. Animals and humans are infected by *Alpha* and *Beta* coronaviruses whilst birds are infected by *Delta* and *Gamma* coronaviruses [4].

Human coronaviruses such as HCoV-NL63, HCoV-HKU1, HCoV-229E and HCoV-043 have been previously associated with upper respiratory tract infections in immunocompromised subjects, children and the elderly [5]. Coronaviruses have been brought into the wider public health prominence due to the evidence of interspecies transmission of zoonotic coronaviruses which has led to outbreaks of a distinct type of human infection characterized by severe respiratory compromise. The novel coronaviruses that have been associated with severe respiratory disease in humans in recent times include Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1), Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). This review highlights the salient clinical diagnostic and epidemiologic features of MERS-CoV and SARS-Co-V-1 infections as seen during pregnancy.

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Immunology

Higher morbidity is suggested when viral infections occur during the course of pregnancy and this may be due to the immune modifications of pregnancy, related to hormone and cell-mediated responses [6]. However, the range of such effects appear to vary between different viruses. Factors such as patients' age, host cell receptors, structural and accessory proteins and cumulative viral load may also play a contributary factor in the degree of illness and likelihood of progression to multi-organ dysfunction [1,7].

The appearance of the novel coronaviruses appears to have followed a striking pattern and unearthed management issues that Obstetric care providers appeared least prepared to promptly address. Infection with Coronaviruses are of also concern because the presenting features are similar to that due to many other viral infections (such as H1N1 and seasonal Influenza infections), creating a diagnostic and management challenge during pregnancy, particularly in winter.

The immune response in normal pregnancy is strikingly similar to what happens with SARS-CoV-2 infection, comprising an increase in Angiotensin converting enzyme 2 (ACE2) receptors, a decrease in natural killer cells, a rise in numbers of NKG2A receptors, a fall in lymphocyte count and an increase in activity of pro-inflammatory factors [2,8,9]. However, specific immune aspects of infection or colonization with the coronaviruses, particularly SARS-CoV-2 are yet to be completely understood. The findings from a recent systematic review showed a robust immune response, characterized by a rise in antibody titre for HCoV-229E, MERS-CoV, SARS-CoV and SARS-CoV2 in the second to third week after illness onset and that emerging human coronaviruses can induce cross-reactive binding antibodies toward endemic phenotypes [10].

The coronaviruses have been shown to suppress a Type I Interferon (IFN) response, while many cytokines, c-reactive proteins and neutrophils are elevated in patients infected by SARS-CoV-2 [10,11].

The characteristic cytokine storm described with SARS-CoV-2 had been described with other coronaviruses before now, but it is remains unclear why B-lymphocytes counts do not seem affected by the coronaviruses [10]. This may become a potential direction of research with regards to response to targeted or co-incidental immunization.

Middle east respiratory syndrome coronavirus (MERS-CoV)

The Middle East Respiratory Syndrome Coronavirus (MERS-CoV) is a lethal zoonotic infection which was first reported in 2012 after isolation from a hospitalised patient in Saudi Arabia with severe respiratory compromise [12,13]. It is a beta coronavirus in the same family as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1), but the World Health Organization adopted the nomenclature of MERS-CoV for consistency and uniformity of reporting. The literature and data on MERS-CoV and pregnancy is limited to a few case reports and case series from Saudi Arabia, South Korea, United Arab Emirates and Jordan [14–16].

Epidemiology

Since the first reported case until the end of January 2020, a total of 2519 confirmed cases of MERS-CoV had been reported to the WHO, with the majority of these cases diagnosed in Saudi Arabia [17]. MERS-CoV remains a high priority pathogen for the global health community because of its pandemic potential and the significant case fatality rate of 34.3% [17]. MERS-CoV continues to cause intermittent sporadic cases in the Middle East as well as nosocomial outbreaks, thus underpinning the substantial risk of widespread global spread with the current ease of global travel [18,19]. Evidence now exists that Dromedary camels are the host reservoir species for MERS-CoV and that transmission from these camels to humans has been documented [20].

Approximately 25% of cases of MERS-CoV were attributable to either direct or indirect contact with the host reservoir (Dromedary camels) whilst about 50% of cases were linked to nosocomial (healthcare associated) outbreaks involving healthcare workers, patients and visitors to facilities with positive cases [21,22]. More severe cases were seen in older males with underlying medical conditions, especially diabetes, chronic respiratory and kidney diseases [19].

Pathogenesis

MERS-CoV is a large single stranded RNA virus with a genome that encodes for a large number of proteins, potentially enhancing its adaptability and cross-species infectivity. The spike proteins play a crucial role in binding to the host's cellular receptor which has been identified as Dipeptidyl peptidase 4 (DDP4) [23,24]. The DDP4 receptors are relatively more abundant in the lower airways compared to the upper airways with greater expression in the non-ciliated bronchial epithelial cells as well as Type 1 and 2 pneumocytes and MERS-CoV, unlike SARS-CoV-1, does not target the ACE2-expressing ciliated epithelial cells [19].

Clinical course and outcome in pregnancy

The clinical presentation and symptom profile in pregnant women appear to be similar to the non-pregnant adult population with MERS-CoV infection [25,26]. The incubation period ranges from 2 to 14 days with a mean of 5.2 days (95%CI 1.9–14.7) in hospital-associated clusters [27]. The leading presenting symptoms of MERS-CoV are fever, cough, shortness of breath, myalgia, diarrhoea and vomiting [19,21]. Majority of the diagnosed cases were symptomatic, with fewer asymptomatic cases are identified through contact tracing of exposed individuals [26].

The diagnosis of MERS-CoV is by Reverse Transcriptase-Polymerase chain reaction (RT-PCR). Although upper respiratory tract samples are much easier to obtain, they are more likely to yield inconclusive or negative results due to sampling limitations. The physiological changes in the upper airway in pregnancy may add to sampling challenges. Sampling from the lower respiratory tract, specifically fresh bronchoalveolar aspirate is the most reliable test sample for diagnostic processing. Additional diagnostic features associated with MERS-CoV include abnormal chest radiographs (X-ray and CT scan), leukopenia, lymphopenia, thrombocytopenia, elevated LDH, AST and ALT [21]. The disease runs a severe course in the majority of reported pregnant and non-pregnant population, with up to 89% requiring ICU admission and 72% requiring ventilation [19,25,27]. Disease progression in severe cases is complicated by single or multi-organ failure, commonly respiratory, renal and liver failure.

Maternal and fetal outcome

In a published series of 11 pregnant women with MERS-CoV by Alfuraj *et al*, most of the patients appear to have contracted the infection through exposure to an infected person either within the household or hospital setting and there was only one case of primary infection following a visit to a camel barn [26]. In the series, the mean maternal age and gestational age with standard deviation at the time of diagnosis of MERS-CoV were 33.7 +/- 4.3 years

and 26.3 +/- 9 weeks and 64% (7/11) were multigravida. As in non-pregnant population, most of the pregnant women (64%) had severe disease necessitating ICU admission, with a mortality rate of 27% (3/11). There was no consistent association with pre-existing disease in the fatalities, probably due to the younger age group of the subjects. Most the cases (9/11) were diagnosed in the second and third trimesters with preterm delivery in 45% (5/11), vaginal delivery in 63% (7/11) and fetal loss in 3 patients (27%); which occurred at 20, 24 and 34 weeks of pregnancy [25,26].

The overall disease profile in terms of severity, admission to ICU and mortality appear to be similar to what obtains in the non-pregnant population with MERS-CoV.

Treatment and prevention

There has been no therapy or vaccination for the treatment or prevention of MERS-CoV infection. The approach to clinical management is focussed on supportive treatment with symptom alleviation and management of acute severe respiratory distress, respiratory failure and multi-organ failure in severe disease. A number of therapies have been used in the past, including antivirals (interferons, ribavirin, lopinavir-ritonavir), convalescent plasma and extracorporeal membrane oxygenation [28,29,30].

In the absence of effective treatment or vaccine, preventive strategies should be prioritised for pregnant women and the general population at large especially in high-risk regions. A combination of well-integrated measures is required to reduce risk of future outbreaks.

General preventive measures include personal and environmental hygiene, strict infection prevention and control measures in healthcare facilities, prompt isolation of confirmed cases and contact tracing during suspected outbreaks.

MERS-CoV specific preventive measures include pasteurisation of camel milk, or better still, the avoidance of ingestion of raw camel meat and dairy. Pregnant women should reduce exposure and contacts with dromedary camels and observe basic hand hygiene practices particularly in high-risk settings. Re-organisation of obstetric care services during period of MERS-CoV outbreaks may be necessary to avoid widespread infection. This may necessitate pooling of cohorts of infected patients together in designated facilities to reduce widespread infection across the healthcare facilities.

MERS-CoV infection in pregnancy is uncommon but carries significant maternal and perinatal mortality, hence concerted efforts should be devoted to the search for effective treatment and vaccine development. The closeness of the host reservoir to humans in parts of the world highlights the risk of MERS-CoV as the pathogen capable of a future pandemic; constant vigilance is required to mitigate this threat.

Severe Acute respiratory Syndrome Coronavirus (SARS-CoV-1)

The first cases of severe acute respiratory syndrome (SARS-CoV-1) were noticed in 2002 [31]. The causal pathogen was eventually identified as a novel coronavirus and by the time of its containment by 2004, over 8447 cases had been reported with 813 deaths (9.6%) in 33 countries [7,32].Of note, 21% of the infections had occurred in healthcare workers [33].

Epidemiology

Two major outbreaks of SARS-CoV-1 occurred between 2002 and 2004, in the same region of the same country between 2003 and 2004. Additional clusters of cases occurred in 2003 in Taiwan, Singapore and China [34]. The masked palm civet was identified as the amplification host for SARS-CoV-1, and the epidemic is believed to have resulted from civet-human contacts in Chinese animal markets and this is supported by the finding of identical viral isolates in both the animals and infected humans [7,31]. A case fatality of 13.2% was reported in patients below the age of 60 [4,35]. Healthcare workers (HCW) were particularly affected during the SARS-CoV-1 outbreaks and the risks associated with HCW infection include performance of high-risk procedures, inconsistent use of personal protective equipment (PPE) and reusing items such as stethoscopes and goggles [33,34].

The incubation period of SARS-CoV-1 averages 6.4 days (2 to 10 days) and the spread is mainly through respiratory droplets [31]. Although the virus has been isolated in various body fluids the highest concentration of the virus was isolated in the lungs and small bowel and this is possibly related to the high concentration of SARS-CoV-1 receptors in these areas [31,36].

Clinical course in pregnancy

The presenting symptoms of SARS-CoV-1 in pregnancy are similar to the non-pregnant population with the dominant symptoms being fever, non-productive cough, myalgia and general malaise [37]. Watery diarrhoea is present in up to 20% of patients with progression to dyspnoea, respiratory failure and death [34]. The laboratory findings associated with SARS-CoV-1 infection include lymphopenia and raised lactate dehydrogenase levels [38,39]. Nasopharyngeal aspirates and throat swabs are used in diagnostic testing using RT-PCR particularly in the early stage of the infection. In patients with diarrhoea, stool sampling provides alternative source for viral isolation. The quantitative RT-PCR has been used to measure viral load in nasopharyngeal aspirate and the level of viral load appear to correlate with the likelihood of oxygen desaturation and the need for mechanical ventilation [34]. Radiological findings in infected patients include abnormal chest radiographs and new infiltrates on CT scan. The presence of other comorbidities such as diabetes increases the risk of death. Other predictors of severe illness include advanced age, neutrophilia and elevated lactic dehydrogenase [34,37,39,40].

Maternal and fetal outcome

The evidence regarding maternal and fetal outcome in SARS-CoV-1 infection during pregnancy is limited to few published case reports and case series. In the series of 12 pregnant women with SARS-CoV-1, the infection was associated with an increased risk of miscarriage, preterm delivery and likely association with intrauterine growth restriction [40]. In addition, 25% mortality was reported (3/12) with a higher need for endotracheal intubation compared to non-pregnant patients but there was no evidence of vertical or parental transmission in the published case series [34,41].

Treatment and prevention

No treatment exists for SARS-CoV-1 the infection during pregnancy. Intravenous Ribavirin was administered to 11 of the 12 pregnant patients treated in Hong Kong with no clear evidence of benefit. Indeed, there are concerns that treatment with Ribavirin could have been harmful given that the reported cases of SARS-CoV-1 in North America were not treated with Ribavirin and both had good maternal and fetal outcome [38,40,41]. The lack of specific treatment modality underlines the importance of preventive measures. The containment of SARS-CoV-1 infection from escalating into a pandemic was most probably due to the rapid introduction of complimentary public health interventions. These include

travel advisory and public education, isolation of infected patients in designated facilities as well as contact tracing, border surveillance and quarantine practices [37]. There was also strict adherence to appropriate use of personal protective equipment (PPE), limitation of visitors to maternity units and service reorganisation to reduce mixing of infected with non-infected patients [39,41,42,43].

Conclusion

There have been several outbreaks of viral infections over the last decade. These infections have increasingly posed a significant risk to women by virtue of their altered physiology and increased susceptibility. There are currently no standard effective drug therapies for these infections but management should include a multidisciplinary team of obstetricians, virologists and anaesthetists.

At least 13 vaccines against MERS-CoV are under development [44]. Given the infrequent occurrence of the two coronaviruses in question, the comparatively sub-endemic levels involving pregnant women and the uncertainty over the possible adverse effects of administering new vaccines, it is unlikely that *peri*-conceptional and pregnant women would immediately be eligible.

Adaptive systems which enable structured collection of information on (affected) pregnant women during epidemics have been advocated [45]. We are of the opinion that such tools also have a role in small isolated outbreaks, of upper respiratory of systemic viral illnesses, especially when pregnant women appear to be disproportionally represented.

An important aspect of management is ensuring that staff are effectively protected.

With regards to prevention, information, education and communication strategies must be deployed and shared across geographical borders so as to efficiently track and trace both pregnant and non-pregnant patients of infections suspected to have triggered a mini outbreak including novel coronaviruses.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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