


## SPECIAL ISSUE ARTICLE

# COVID-19 and hydatidiform mole

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## Abstract

The emergence of coronavirus disease 2019 (COVID-19) as a pandemic threatens the entire world resulting in severe consequences for people's health. Pregnant patients with COVID-19 had immune dysregulation that could result in abnormal pregnancy outcomes such as hydatidiform mole (HM), recurrent pregnancy loss, and early-onset preeclampsia. In this article, we tried to summarize the possible association between COVID-19 and the HM's development by reviewing the role of NOD-Like Receptor (NLR) Family Pyrin Domain Containing 7 (NLRP7), cytokines, zinc, and leukocytes in the pathogenesis of HM.

## KEYWORDS

coronavirus, COVID-19, Gestational trophoblastic diseases, Hydatidiform mole

## 1 | INTRODUCTION

Coronaviruses are one of the Coronaviridae family in the Nidovirales order. Coronaviruses are small in size (65-125 nm in diameter) and contain a single-stranded RNA as a nucleic material. They are characterized by having crown-like spikes on the virus' outer surface; thus, it is named coronavirus.<sup>1</sup> The coronaviruses are genotypically and serologically divided into four subgroups:  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -CoVs. Human CoVs infections are mainly due to  $\alpha$ - and  $\beta$ -subgroups like severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), which belong to  $\beta$ -CoVs.<sup>2</sup>

The SARS-CoV-2 virus causing the coronavirus disease 2019 (COVID-19) was classified by the World Health Organization (WHO) as a  $\beta$ -CoV of group 2B.<sup>3</sup> The genetic sequence of SARS-CoV-2 showed more than 80% identity to SARS-CoV and 50% to the MERS-CoV; both originate in bats.<sup>4,5</sup>

Presently, COVID-19 patients are considered to be the primary source of infection, as person-to-person transmission occurs

predominantly via direct contact or through droplets during coughing or sneezing.<sup>6</sup> Until now, there is no proof that SARS-CoV-2 can be transmitted through aerosols or from mother to baby during pregnancy or childbirth.<sup>6</sup> Hence, there are no available data on the consequences of COVID-19 on the course and outcome of pregnancy; it is crucial to pay more attention to this issue, especially that COVID-19 still appears to be sweeping. Moreover, pregnant mothers are pretty more predisposed to infection by respiratory pathogens and severe pneumonia.

## 2 | IMMUNOLOGY AND PATHOGENESIS OF COVID-19

All coronaviruses have specific genes in ORF1 downstream regions that encode proteins for viral replication, nucleocapsid, and spikes formation, and the structural proteins are encoded by the four structural genes, including spike (S), envelope (E), membrane (M), and nucleocapsid (N) genes.<sup>7</sup> Although the genome of the SARS-CoV-2 has

been reported over 80% identical to the previous human coronavirus (SARS-like bat CoV), there are remarkable variations in SARS-CoV and SARS-CoV-2 such as the absence of 8a protein and fluctuation in the number of amino acids in 8b and 3c protein in SARS-CoV-2.<sup>8</sup>

Interestingly, the SARS-CoV-2 shares the SARS-CoV in using ACE2 (angiotensin-converting enzyme 2) cell receptor for the entry to host cell.<sup>9</sup> ACE2 is a type I membrane protein expressed in lung, heart, kidney, and intestine mainly associated with cardiovascular diseases.<sup>10</sup> It also affords a direct binding site for the S proteins of CoVs.<sup>11</sup> It is thought that a single N501T mutation in SARS-CoV-2's spike protein leads to a significant boost in the binding affinity of SARS-CoV-2 S protein for ACE2 by 10- to 20-fold higher than SARS-CoV.<sup>12</sup>

The binding of a receptor expressed by host cells is the first step of viral infection followed by fusion with the cell membrane. Then, the viral genome begins to replicate after the virus successfully enters the cells; its genome is released into the cytoplasm and is translated into two polyproteins and structural proteins.<sup>11</sup> Whereas the virus enters the cells, its antigen will be presented to the antigen presentation cells (APC), which is a central part of the body's antiviral immunity. Antigenic peptides are presented by major histocompatibility complex (MHC; or human leukocyte antigen [HLA] in humans) and then recognized by virus-specific cytotoxic T lymphocytes (CTLs). The antigen presentation of SARS-CoV mainly depends on MHC I molecules, but MHC II also contributes to its presentation.<sup>13,14</sup>

Antigen presentation subsequently stimulates the body's humoral and cellular immunity, mediated by virus-specific B and T cells. Similar to common acute viral infections, the antibody profile against the SARS-CoV virus has a typical pattern of IgM and IgG production. The SARS-specific IgM antibodies disappear at the end of Week 12. In contrast, the IgG antibody can last for a long time, which indicates that the IgG antibody may mainly play a protective role.<sup>15</sup> Lymphocytopenia is considered one of the most prominent markers of COVID-19 as both T cells and NK cells were reduced. The percentage of CD8 + T-cell reduction was 28.43% and 61.9% in the mild and severe group, respectively, and the NK cell reduction was 34.31% and 47.62%, respectively, in mild and severe groups.<sup>16</sup>

Furthermore, the expression of HLA-DR in CD4 + and CD8 + cells was increased, which indicates that although patients have lymphopenia, the lymphocytes are in extreme activation.<sup>16</sup> Also, CD4 + CCR4+CCR6 + Th17 cells increased, and the cytotoxic particles such as perforin and granulysin were highly expressed in CD8 + T cells.<sup>17</sup> Most of the severely infected COVID-19 patients show an elevation in their cytokine profile resembling cytokine storm detected in SARS and MERS, as the levels of IL-1B, IL-1RA, IL-7, IL-8, IL-9, IL-10, fibroblast growth factor (FGF), granulocyte-macrophage colony-stimulating factor (GM-CSF), IFN $\gamma$ , granulocyte colony-stimulating factor (G-CSF), interferon- $\gamma$ -inducible protein (IP10), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein-1 alpha (MIP1A), platelet-derived growth factor (PDGF), tumour necrosis factor (TNF- $\alpha$ ), and vascular endothelial growth factor (VEGF) were elevated in their sera.<sup>18</sup>

Cytokine storm states an extreme and abandoned release of proinflammatory cytokines (IFN- $\alpha$ , IFN- $\gamma$ , IL-1b, IL-6, IL-12, IL-18, IL-33, TNF- $\alpha$ , TGF- $\beta$ , etc) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc) by immune effect or cells.<sup>19</sup> SARS-CoV-2 infects target cells through ACE2. There is no ACE2 expression on lymphocytes, so these lymphocytes are probably destroyed by cytokine storm, not by the invasion of the virus itself. Hence, cytokine storm may increase the severity of immunological attack against the body itself via gush of excess cytokines without regulating lymphocytes resulting in many hazardous effects as adult respiratory distress syndrome (ARDS), multiple organ failure, and finally lead to death in severe cases of SARS-CoV-2 infection.<sup>17</sup>

### 3 | IMMUNOLOGY AND PATHOGENESIS OF HYDATIDIFORM MOLE

Hydatidiform mole (HM) is a relatively rare gynecologic condition resulting from an abnormally fertilized egg and mostly occurs in primigravida.<sup>20</sup> It is characterized by placental overgrowth, while the embryonic development is markedly abnormal or absent. There are two types: complete (CHM) or partial (PHM) according to the histopathological classification. The placentas of both CHM and PHM are categorized by edematous swelling of the chorionic villi and trophoblastic hyperplasia. The incidence of CHM is around 1/1000 pregnancies, and PHM around 3/1000.<sup>21</sup> HM is a non-malignant form of gestational trophoblastic diseases (GTDs) associated with abnormally elevated human chorionic gonadotropin (hCG) level.<sup>22</sup> There are many risk factors are involved in the occurrence of HM such as uterine abnormalities, defects in the ova, folic acid deficiency, extreme maternal age (more than 35 years or less than 20 years), previous molar pregnancy, history of oral contraceptive use, deficiency of beta-carotene or animal fat and smoking.<sup>23</sup>

Previous reports showed that the decidual immune cell infiltrates especially FoxP3 + regulatory T cell and CD3 + T cells, are significantly higher in HM than found in a healthy pregnancy.<sup>24,25</sup> Also, there is a marked elevation of serum level of proinflammatory cytokines such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$  and a significant increase of C-reactive protein in HM compared with healthy pregnancy.<sup>26</sup> However, the immunology of HM is still mysterious and not clearly understood.

Indeed, Alex et al 2002 committed that human papillomavirus (HPV) infection seems to be associated with CHM considerably. In contrast, human immunodeficiency virus (HIV), cytomegalovirus (CMV), or herpes simplex virus (HSV) revealed no association with the pathogenesis of this disease.<sup>27</sup> It has been shown in previous studies that SARS infection during pregnancy can trace to high rates of spontaneous abortion, premature birth, and intrauterine growth restriction. Nevertheless, there is no proof of vertical transmission of SARS infection from the mother to the child or any evidence that SARS may affect the embryo implantation and cause HM.<sup>28</sup> Therefore, there are no available reports about the association between coronaviridae family and HM.

## 4 | ROLES OF NOD-LIKE RECEPTOR FAMILY PYRIN DOMAIN CONTAINING 7

Previous studies reported some mutations in Family Pyrin Domain Containing 7 (NLRP7) protein in 48-80% of patients with recurrent HMs.<sup>29</sup> NLRP7 has a role in pathogen-mediated inflammation and apoptosis, so it is the dominant gene associated with recurrent HMs.<sup>30</sup> NLRP7 is one of the nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) family of proteins, a type of cytoplasmic pattern recognition receptor that recognizes intracellular danger signals and initiates inflammatory responses to fight them. For NLRP7, its inflammasome accumulates due to several stimuli like bacteria (gram-negative *Legionella pneumophili*, *Archoleplasma laidlawii*, *Staphylococcus aureus*), *Mycoplasma* species and *Mycobacterium bovis*.<sup>31,32</sup> The overexpressed normal NLRP7 interacts with ASC, caspase-1, and IL-1 $\beta$  and downregulates IL-1 $\beta$  production within the inflammasomes. This could explain the possibility that bacterial or viral infections like SARS-CoV-2 can mediate HM in pregnant women.

## 5 | ROLES OF CYTOKINES

Cytokines are a group of peptide mediators up and down regulate the immunological, inflammatory, and reparative host responses to injury.<sup>33</sup> They are non-antibody soluble products of activated lymphocytes (lymphokines) and macrophages (monokines) acting as intracellular growth signals that regulate local and systemic inflammatory responses.<sup>34</sup> Interestingly, the lymphocytes and macrophages in the female genital system secreting soluble factors affecting the embryo development and trophoblast growth.<sup>35</sup> As the fetal trophoblast stimulates the release of maternal cytokines, it stimulates trophoblast function and growth.<sup>36</sup>

Placental cells produce different cytokines as IL-1, IL-2, IL-6, IFN- $\alpha$ , IFN- $\gamma$ , and TNF- $\alpha$ .<sup>33</sup> However, cytokines could have an essential role in the immunological failure of normal implantation. At the time, the maternal immune system combats in creating and preserving tolerance to the allogenic fetus while conserving the ability for protection against microbial challenges. Hence, it was found that pregnancy prompted a vigorous and significant increase in endogenous STAT5ab signaling across multiple T-cell subsets, including CD25 + FoxP3+ Treg cells, naive and memory CD4 + and CD8 + T cells, and  $\gamma\delta$  T cells. However, the maternal innate immune cells, such as NK cells and monocytes, are well prepared to guard the invasion of foreign pathogens, respond more strongly to viral pathogens, even though some adaptive immune responses are down-regulated during pregnancy, for example, decreased numbers of T and B cells.<sup>37</sup>

As the activation of endometrial lymphocytes and macrophages by non-reproductive tissue-specific antigens such as bacteria or viruses could lead to the unsuitable environment for the implanting embryo by releasing variable cytokines including interleukin 1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), interferon  $\tau$  and  $\gamma$  (IFN $\tau$ ),

and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ).<sup>38</sup> Therefore, we supposed that COVID-19 infection, which is characterized by a cytokine storm and by raise IL-2, IL-7, GM-CSF, and TNF- $\alpha$  level, may affect the normal implantation and induce the development of HM. On the other hand, miscarriage as an example may be characterized by reduced TNF- $\alpha$  and IL-10 in sera of affected mothers compared with healthy pregnancies.<sup>39,40</sup> Therefore, there is a significant similarity in the cytokine profile between COVID-19 and HM, much more specific than other pregnancy outcomes.

## 6 | ROLE OF ZINC

Metal ions as zinc and copper are essential for biological systems, especially in embryonic and fetal development.<sup>41</sup> Zinc plays a role in cellular growth and is necessary for protein synthesis, like intercellular DNA, RNA, and cell division.<sup>42</sup> It is also reported that there are significantly lower serum levels of zinc in HM patients compared with healthy pregnant women which may be a contributor in its pathogenesis.<sup>43</sup> Meanwhile, zinc has an essential role as a protective and adjuvant therapy for COVID-19, mainly by reducing the inflammation and modulating antiviral and antibacterial immunity.<sup>44</sup>

Moreover, zinc is thought to have anti-inflammatory activity by inhibiting NF- $\kappa$ B signaling and modulation of regulatory T cells and restricting the cytokine storm.<sup>44</sup> Therefore, we want to highlight the role of zinc in COVID-19 patients, as its deficiency may affect the embryonic development and predisposes to HM occurrence.

## 7 | ROLE OF LEUKOCYTES

In a healthy pregnancy, there is a physiological leucocytosis that resulted from the inflammatory process induced during the implantation phase. Leukocyte activation and expression of various adhesion molecules on activated leukocytes occur at the beginning of pregnancy.<sup>45</sup> These cells secrete GM-CSF that helps trophoblastic invasion. On the other hand, there is leucopenia in patients with HM which is characteristic for it unlike miscarriage that is significantly associated with a high leukocytic count in the first trimester with a significant increase in peripheral NK and T cells and its activity.<sup>46,47</sup>

Leucopenia is due to a more reduced inflammatory function that enhances the trophoblastic invasion.<sup>48</sup> Besides, the percentage and absolute counts of lymphocytes are significantly low in patients with HM.<sup>49</sup> The relation between WBC count and HM could be attributed to inadequate placentation in HM that results from the absence of villous development and cytotrophoblastic invasiveness.

Leucopenia is one of the key features for diagnosing COVID-19 patients due to the effect of secondary hemophagocytic lymphohistiocytosis induced by viral infections<sup>50</sup>; therefore, a causative association could be proposed between COVID-19 and the development of HM.

## 8 | CONCLUSIONS

In conclusion, the full pathogenesis and immunological aspects of HM are still mysterious. Future researches should try to elaborate on the association between COVID-19 and the development of HM. The main limitation of the current concept of our review is the lack of studies or case reports reported a positive patient of COVID-19 with HM. No available RNA-PCR for cases of HM to detect COVID-19 infection in our developing country. Until the availability of further studies, and as there is no universal screening for COVID-19, we suggest that obstetricians should be aware of the probability of occurrence of HM among positive COVID-19 pregnant women or those contagious to a positive COVID-19 patient.

### CONFLICT OF INTEREST

The authors state that there are no conflicts of interest.

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